The Journal of Allergy

VOL. 7 JULY, 1936 NO. 5

Original Articles

REACTIONS TO INTRACUTANEOUS INJECTIONS OF NUCLEOPROTEINS OF THE UPPER RESPIRATORY PATHOGENIC BACTERIA IN ASTHMATIC PATIENTS

FRANKLIN A. STEVENS, M.D., AND LEOPOLD JORDANI, M.D.
NEW YORK, N. Y.

INTRACUTANEOUS tests with bacteria or with bacterial extracts have been employed by Goodale,[1] Walker,[2] Rackemann and his coworkers,[3] and Thomas and Touart[4] to determine the bacterial sensitivity of asthmatic patients. Various types of cutaneous reactions, both immediate and delayed, following scratch tests or intracutaneous inoculation, have been considered indicative of bacterial sensitization. Immediate reactions resembling the wheal obtained in pollen sensitive patients and delayed tuberculin-like reactions have been described. The delayed reactions have been described as indurated, papular, erythematous or as associated with sterile lymphangitis. After determining the specific cutaneous bacterial reactivity of the patient either with stock strains or with autogenous vaccines prepared from cultures from a patient, inoculations with the vaccines with which reactions were obtained have been carried out. The reports concerning the reliability of the tests as determined by the results of the subsequent treatment have been favorable. Cooke,[5] however, has denied that such tests are of value. In a critical analysis of Walker's data, he could find no evidence that the cutaneous reactions indicated the bacteria specifically responsible for the asthma and pointed out that the mechanism by which bacteria caused asthma was different from the mechanism in pollen or protein sensitive patients.

Asthmatic patients in this clinic have been tested with solutions of bacterial nucleoprotein over a period of several years. The proteins were prepared from broth cultures of bacteria which were centrifuged, washed with acetone, dried, ground in a ball mill, and then extracted in weak alkali. The ground bacteria were suspended in distilled water which was made alkaline with sodium hydroxide to a pH of 8.0 to 8.5. This suspension was agitated frequently, centrifuged, and the protein was then precipitated from the clear supernatant fluid by the addition

From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital.

of acetic acid. The precipitate was dissolved in alkali and reprecipitated with acid seven times. A small part of the protein became insoluble with each precipitation. This protein probably corresponds to the D and E fractions obtained from streptococcus by Heidelberger and Kendall.[6] The nitrogen concentration in the final solution was determined, and dilutions containing 1 mg. N in 100 c.c. of solution were prepared for intracutaneous testing. Intracutaneous injections of 0.05 c.c. of these dilutions were given. Patients were tested frequently with the proteins of *Micrococcus catarrhalis, Streptococcus viridans, Streptococcus hemolyticus, Bacillus influenzae,* and *Staphylococcus aureus.* Both immediate and delayed reactions occurred at the sites of the injections. The immediate reactions appeared in a few minutes and disappeared within an hour. They consisted of a zone of erythema surrounding a raised white central area 1 to 2 cm. in diameter. This central zone had irregular edges, but definite pseudopodia were not observed. In the following tables only reactions with this central zone and a surrounding area of erythema at least 2 cm. in diameter have been recorded as positive immediate reactions. The delayed reactions were erythematous and occasionally were raised and indurated. Some delayed reactions made their appearance within six hours; all reached their intensity in twenty-four hours; and those which were especially indurated persisted two or three days. None of these reactions were purpuric or papular. Only one peculiar reaction was encountered. Here, an eruption resembling erythema multiforme appeared at the site of inoculation with *Micrococcus catarrhalis,* and subsequently, when retested, a similar eruption recurred in the region of the old sites of inoculation. Tests to all five extracts were done at the same time on the forearms and observed at the end of a half hour and again the following day. The negative tests served as controls. Tests have also been done with pneumococcus protein and with purified type specific carbohydrates, but these results will be reported separately in a study of another phase of the problem.

In previously reported analyses of the cutaneous reactions with bacteria or their extracts, the data have been studied without regard to the type of asthmatic patient, i.e., as to whether he was generally sensitive or non-sensitive to common allergens. The first analysis reported here is one of 100 patients who were tested between the months of November, 1933, and March, 1934. In this analysis of 100 consecutive admissions to the clinic, the reactions have been considered from the standpoints of whether they were immediate or delayed, as to the size of the reaction in centimeters, and as to whether or not they occurred especially in patients who were sensitive to common allergens. These data have been arranged in Table I. All reactions under 2 cm. in diameter have been omitted because reactions of a lesser diameter might possibly be purely irritative ones from the intracutaneous injection. Only the

essential facts need be summarized. They are as follows: Reactions, both immediate and delayed, are most common with *Micrococcus catarrhalis* protein, and occur in decreasing order of frequency with *Staphylococcus aureus, Streptococcus hemolyticus, Bacillus influenzae,* and *Streptococcus viridans* proteins. Second, the fact that the patients were of the sensitive or non-sensitive type with other allergens has no influence on the distribution of the bacterial reactions among these patients. The total number of reactions to the bacterial proteins, i.e., the delayed and immediate combined, were distributed in proportionate percentages between the sensitive and the non-sensitive groups. Third, immediate and delayed reactions were observed in both groups. Although the immediate reactions exhibited a slight tendency to occur in the sensitive group, the total number of reactions is too small to substantiate this point.

TABLE I

IMMEDIATE AND DELAYED SKIN REACTIONS IN ONE HUNDRED CONSECUTIVE ADMISSIONS

BACTERIAL PROTEIN	TYPE OF REACTION	2 CM.	3 CM.	4 CM.	31 (31%) SENSITIVE PATIENTS	69 (69%) NON-SENSITIVE PATIENTS	TOTAL REACTIONS
Influenza	Immediate	7	1		2 (25%)	6 (75%)	8
	Delayed	11	2	4	4 (24%)	13 (76%)	17
Mic. catarr.	Immediate	4	4	3	6 (54%)	5 (46%)	11
	Delayed	19	11	13*	13 (30%)	30 (70%)	43
Strep. vir.	Immediate	5	3		5 (63%)	3 (38%)	8
	Delayed	2	2		1 (25%)	3 (75%)	4
Staph. aur.	Immediate	16	11	1	12 (23%)	16 (77%)	28
	Delayed	7	1	1	6 (66%)	3 (33%)	9
Strep. hem.	Immediate	8	5		6 (46%)	7 (54%)	13
	Delayed	5	6	4	3 (20%)	12 (80%)	15
All bacteria	Immediate	40	24	4	31 (45%)	37 (54%)	68
	Delayed	44	22	22	27 (32%)	61 (69%)	88
Total reactions		84	46	26	58 (37%)	108 (63%)	166

*Four cm. or larger.

Because numerous reactions to proteins extracted from foods and inhalants are frequently observed on the same patient, the tests done with the bacterial proteins on the admission of these 100 patients to the clinic have been analyzed further to determine whether multiple reactions occurred in patients who were sensitive to the common allergens. This analysis has been made in Table II, in which the patients have been separated into the sensitive and non-sensitive groups; 31 in the first and 69 in the second, and again subclassified as to the number who showed one, two, three, and four or more reactions to bacteria. Those with immediate or delayed reactions alone and those with both immediate and delayed reactions have been segregated in separate columns. As might be anticipated, the more bacterial reactions occurring with the proteins on testing the same patient the greater the tendency for the

patient to show both immediate and delayed reactions, but there is no tendency for the patients in the sensitive group to show multiple bacterial reactions more frequently than in the group not sensitive to the common allergens. Eighteen of 31 sensitive patients showed immediate bacterial reactions. These figures are to be compared with a total of 25 who showed immediate reactions among the 69 in the non-sensitive group.

TABLE II

DISTRIBUTION OF PATIENTS ACCORDING TO THE NUMBER OF BACTERIAL REACTIONS IN THE SENSITIVE AND NON-SENSITIVE GROUPS

TOTAL NO. OF BACTERIAL REACTIONS SHOWN BY PATIENTS	31 PATIENTS SENSITIVE TO COMMON ALLERGENS			69 PATIENTS NOT SENSITIVE TO COMMON ALLERGENS		
	IMMEDIATE ONLY	IMMEDIATE AND DELAYED	DELAYED ONLY	IMMEDIATE ONLY	IMMEDIATE AND DELAYED	DELAYED ONLY
None 20 patients		(No bacterial reactions 3)			(No bacterial reactions 17)	
One 33 patients	7		6	7		13
Two 30 patients		6	4		9	11
Three 12 patients		2			7	3
Four or more 5 patients		3			2	
Total patients in groups	7	11	10	7	18	27

While the statistics on these 100 patients were being accumulated, the observation was made that although immediate and delayed reactions to different bacteria might occur on the same patient, immediate reactions were seldom followed by delayed reactions at the site of inoculation to the same bacterial protein. In 500 tests, 166 reactions were observed; 58 of these were immediate, and 108 were delayed. On only six occasions were immediate reactions followed by the delayed type of response. Four of these combined reactions were to *Micrococcus catarrhalis,* one to *Streptococcus viridans,* and one to *Streptococcus hemolyticus* protein. All six reactions occurred in four patients, one of whom showed reactions to three bacterial proteins. The other three reacted to *Micrococcus catarrhalis* protein only. Some of these patients were sensitive and others were insensitive to the common allergens. At the present time no explanation of the dissociation of immediate and delayed type of response to the proteins can be offered. One observation may afford a clue to the mechanism; in all instances in which the responses to a bacterial protein were combined, both the immediate and the delayed reactions were 3 cm. or more in diameter. Reactions of this intensity are above the average.

So far the analysis of the reactions to the bacterial proteins has been similar to other analyses reported, i.e., it has been confined to reactions occurring after tests done on patients without a subsequent follow-up to determine the duration of the reactions observed when the patients

TABLE III

VARIATION IN REACTIONS IN NINE PATIENTS TESTED AT INTERVALS

DATE OF TEST	STAPH.		HEM. STREP.		INF.		STREP. VIR.		MICR. CATARRH.	
	I	D	I	D	I	D	I	D	I	D
	CM.		CM.		CM.		CM.		CM.	
11/ 4/33	–	–	–	1	–	–	–	1	–	1
1/22/34	2	–	–	3	–	1	–	2	–	–
5/ 7/34	3	–	–	1	–	–	–	2	–	1
11/23/34	2	–	–	–	–	2	–	–	–	–
1/21/35	–	–	–	–	–	–	–	–	–	–
12/11/33	2	–	–	3	–	–	–	–	–	–
5/21/34	–	–	–	–	–	–	–	–	–	–
12/ 4/33	–	–	–	–	–	–	–	–	–	2
1/10/35	3	–	–	–	–	–	–	–	3	–
12/ 4/33	–	1	–	2	–	–	–	–	–	3
3/ 2/34	–	1	–	–	–	2	–	–	–	3
4/23/34	–	3	–	–	–	1	–	–	–	3
10/13/33	–	–	2	–	1	–	–	–	3	–
5/16/33	–	–	3	–	3	–	–	–	2	–
1/ 8/34	2	–	3	–	–	–	–	–	3	–
3/ 5/34	3	–	3	–	2	–	–	3	3	–
5/21/35	3	–	3	–	–	4	–	3	3	3
1/ 5/34	2	–	–	–	–	–	–	–	–	–
4/30/34	2	–	–	–	–	–	–	–	–	3
6/11/33	–	–	–	–	–	–	–	–	–	3
12/12/33	2	–	–	–	–	–	–	–	–	–
2/ 4/34	–	–	–	2	–	–	–	–	–	–
3/ 7/33	3	–	–	–	–	–	–	–	–	4
10/13/33	–	–	–	–	–	–	–	–	–	–
3/ 9/34	3	–	–	–	–	1	–	–	–	1
5/14/34	3	–	–	–	–	–	–	–	–	2
5/28/34	3	–	–	–	–	–	–	–	–	2
10/25/34	–	–	–	–	–	–	–	–	–	–
1/ 2/35	2	–	–	–	–	–	–	–	–	2
3/ 4/35	–	–	–	–	–	–	–	–	–	3

were first tested. Many of the patients were retested with the same proteins at intervals of two to three months over a period of two or three years. Unfortunately, the results of this follow-up cannot be tabulated because a table containing these data has proved cumbersome and too space consuming. The observations on only a few patients have been arranged in Table III to indicate the results which may be anticipated when tests are frequently repeated.

The following conclusions have been drawn from observations on about 50 patients who were tested repeatedly for two years. First, mild reactions to the bacterial proteins are usually temporary and seldom persist for more than three or four months. This applies to both the immediate and the delayed type of reaction. Second, immediate and delayed reactions bear no relationship to each other chronologically, i.e.,

the immediate reaction is not followed by a delayed reaction to the same bacterial protein and vice versa. Third, large reactions, either immediate or delayed, persist longer than those of moderate intensity. Fourth, reactions of moderate intensity, either immediate or delayed, appear abruptly and usually disappear within a few weeks. On the other hand, a few of these moderate reactions increase in intensity for several months, then gradually become smaller in size and eventually disappear. In a few instances intense immediate reactions to staphylococcus and delayed reactions to *Micrococcus catarrhalis* have persisted several years. Fifth, to summarize, the picture presented by the reactions to these bacterial proteins is one of extreme variability. The picture varies so much and so rapidly that tests done on one occasion furnish little clue to the bacteria to which the patient may react when tested later. The most that may be said is that if a patient reacts intensely to a protein, the same reaction may possibly be obtained several months later.

DISCUSSION

This series of tests was undertaken to determine whether or not tests with bacterial proteins were of value as an indication for specific bacterial therapy. Two types of reactions, an immediate and a delayed type, have been observed. The delayed type is obviously not peculiar to asthmatic patients. It occurs with tuberculin in animals inoculated with tubercle bacillus,[7] appears in animals frequently injected with filtrates of streptococcus[8] or with fractions of the streptococcal bacterial body,[9] is common with streptococcal protein in patients with rheumatic fever[10] who, we assume, have recently been infected with hemolytic streptococcus, and is almost universal with the protein of colon bacillus which is a normal inhabitant of the human intestinal tract. The delayed reaction is apparently a response to bacterial products which may appear in either man or animals following infection, may occur in those harboring a bacterium, or may be induced by inoculations with the fractions of bacteria or with bacterial extracts. At the time the asthmatic patients in this series were tested, 45 surgical patients who had been in the hospital for several weeks and were known to be free from recent infections were tested with the proteins of staphylococcus and hemolytic streptococcus. These patients showed neither immediate nor delayed reactions to these proteins. In view of the accumulated evidence regarding delayed reactions to bacterial proteins, in this series of asthmatic patients it appears that a delayed reaction indicates no more than that a patient has recently been infected with or has harbored a bacterium to which he reacts. In view of the fact that hemolytic streptococcus usually can be cultured from the throats of rheumatic patients for only a short period following the angina[10] which initiates an attack, yet the cutaneous reactions with streptococcal protein may be elicited commonly

long after the attack has subsided, it is obvious that patients may show delayed responses to bacteria which have previously caused infection yet are no longer harbored. The relationship of the immediate reactions to the causation of the asthma in these patients studied is still conjectural and requires further study. For the present the conclusions drawn are that an immediate reaction to a bacterial protein does not depend on a peculiar reactivity of the patient at the time the test is done because immediate and delayed reactions to proteins of different bacteria may be observed in the same patient at the same time. Furthermore, these reactions are but slightly more common in patients showing a general sensitivity to other proteins than in the insensitive group, indicating that the sensitive asthmatic patient is not especially prone to give immediate reactions to bacterial proteins. In general, the immediate and the delayed reactions exhibit the same distribution among these patients and show the same variability over periods of time. A much more extensive investigation is necessary to determine whether these immediate reactions are more common among patients and in families with atopic sensitization than among families and in patients without this particular familial constitutional tendency. Probably, in view of the fact that both immediate and delayed reactions occur so infrequently to the same protein following the same inoculation, groups of patients with diseases such as[10] rheumatic fever and rheumatoid arthritis who show a higher percentage of delayed reactions to streptococcus than the normal will show a relatively low percentage of immediate reactions to the protein of this bacterium.

Dochez and his associates consider that colds are a two-phase infection.[11] Infection with the cold virus is often followed by a bacterial infection of the upper respiratory tract with the common upper respiratory pathogens. Their observations show that the flora during this secondary infection is variable and cannot be predicted with certainty. Even as the flora of the upper respiratory tract may vary among the general population from year to year or may vary with the season of the year, so the flora varies during the bacterial phase of the cold. The flora during this second phase is a reflection of the bacterial flora prevalent at large when the cold is contracted. Inasmuch as asthmatic patients are especially susceptible to upper respiratory infection, they likewise must show from year to year and from season to season great variation in the upper respiratory flora. The delayed cutaneous reaction to bacterial protein is certainly a reaction to infection which is not peculiar to man or to those constitutionally atopic; so that the constantly changing picture presented by these delayed reactions is but an indication of the constantly changing flora in the series of upper respiratory infections to which the asthmatic patients have been subjected. The immediate reaction, too, is a reaction to infection; although its relationship to the asthmatic state has not been determined. These reac-

tions have been as variable as the delayed reactions. The cutaneous reactions then are reflections of generalized reactions to a series of upper respiratory infections caused by a constantly changing bacterial flora.

CONCLUSIONS

1. Immediate and delayed reactions occur when bacterial nucleoproteins are injected intracutaneously in asthmatic persons.

2. Both immediate and delayed reactions at the site of the same inoculation are infrequent.

3. The reactions to the nucleoproteins are constantly changing. During a period of a few weeks positive reactions may disappear and reactions to other upper respiratory bacteria make their appearance.

4. The immediate and the delayed reactions are proportionately distributed among patients sensitive and non-sensitive to the common allergens.

REFERENCES

1. Goodale, J. L.: The Diagnosis and Management of Vasomotor Disturbances of the Upper Air Passages, Boston M. & S. J. **175:** 181, 1916.
The Present Status of Immunization in Hay Fever, Boston M. & S. J. **179:** 293, 1918.
2. Walker, I. C.: Studies on Staphylococcus Pyog. Aureus, Albus and Citreus and Micrococcus Tetragenus and Micrococcus Catarrhalis, J. M. Res. **35:** 373, 1917.
A Clinical Study of 400 Patients With Bronchial Asthma, Boston M. & S. J. **179:** 288, 1918.
The Treatment With Bacterial Vaccines of Bronchial Asthmatics Who Are Not Sensitive to Proteins, J. M. Res. **37:** 51, 1917.
3. Rackemann, F. M., and Graham, L. B.: Vaccine Treatment of Asthma, J. Immunol. **8:** 295, 1923.
Rackemann, F. M.: Relation of Sputum Bacteria to Asthma, J. Immunol. **5:** 373, 1920.
Rackemann, F. M., and Scully, M. S.: The Use of Vaccines in Asthma and Colds, New England J. Med. **199:** 314, 1928.
4. Thomas, L. W., and Touart, M. deM.: Autogenous Vaccine in Diagnosis With Special Reference to Asthma, Arch. Int. Med. **34:** 85, 1924.
Treatment of Asthma With Autogenous Vaccines, Arch. Int. Med. **34:** 79, 1924.
5. Cooke, R.: Studies in Specific Hypersensitiveness; New Etiologic Factor in Bronchial Asthma, J. Immunol. **7:** 147, 1922.
6. Heidelberger, M., and Kendall, F. E.: Protein Fractions of a Scarlatinal Strain of Streptococcus Hemolyticus, J. Exper. Med. **14:** 515, 1931.
7. Baldwin, E. R.: Studies in Immunity to Tuberculosis: Hypersusceptibility or Anaphylaxis, J. M. Res. **22:** 189, 1910.
Krause, A. K.: Studies in Immunity to Tuberculosis: Hypersensitiveness to Tuberculo-Protein and Its Relation to Some Tuberculosis Problems, J. M. Res. **24:** 361, 1911.
8. Stevens, F. A., and Dochez, A. R.: Studies on Biology of Streptococcus: Allergic Reactions With Strains From Erysipelas, J. Exper. Med. **46:** 487, 1927.
9. McEwen, C., and Swift, H. F.: Cutaneous Reactivity to Intradermal Injections of Homologous Indifferent Streptococcus and Its Fractions, J. Exper. Med. **62:** 573, 1935.
10. Coburn, A. F.: The Factor of Infection in the Rheumatic State, Baltimore, 1931, Williams & Wilkins Co.
11. Dochez, A. R., Mills, K., and Kneeland, Yale, Jr.: Disease of the Upper Respiratory Tract, J. A. M. A. **101:** 1441, 1933.
Shibley, G. S., Hanger, F. M., Dochez, A. R., and Mills, K.: Observations of the Normal Bacterial Flora of Nose and Throat With Variations Occurring During Colds, J. Exper. Med. **43:** 415, 1926.

ALUM AS AN ADJUVANT IN SENSITIZING GUINEA PIGS TO RAGWEED POLLEN (AMBROSIA ARTEMISIIFOLIA)*

A. H. W. Caulfeild, M.B., F.R.C.P.(C), M. H. Brown, M.S., B.Sc., and E. T. Waters, B.Sc., Ph.D., Toronto, Canada

DURING the course of a series of experiments[1] for the purpose of analyzing the antigenic components of ragweed pollen, it was necessary to have guinea pigs fully sensitized to ragweed pollen extracts as judged by fatal anaphylaxis.

After preliminary trials, two types of ragweed pollen extract were selected as the most likely to sensitize. They were a solution of ragweed pollen protein and a 5 per cent watery extract of ragweed pollen previously defatted by ether.[1] The sensitizing dose of the protein solution used in a series of experiments varied between 1 mg. and 12.5 mg. and that of the watery extract varied from 0.1 c.c. to 5.0 c.c. The sensitizing dose was given by either the subcutaneous or the intraperitoneal routes. The time interval between the sensitizing dose and the shocking dose varied from 21 days to 101 days. Of 54 guinea pigs so treated, anaphylactic death was induced in 4, anaphylactic reactions of varying severity were recorded in 22, doubtful in 8, and negative in 20. There did not appear to be any correlation between the sensitivity which was induced and the route of injection, the dosage, or the time interval.

It has been reported by Burky[2] that the production of hypersensitive reactions in rabbits to ragweed extracts and other substances was aided by the action of staphylococcus toxin. As a result of this report we prepared a mixture of staphylococcus toxin and ragweed extract. The mixture was made by growing a toxin-producing staphylococcus strain in a medium consisting of equal parts of broth and 5 per cent ragweed extract. The toxin so formed contained approximately 400 hemolytic units per c.c. and was further diluted 1:10 with 5 per cent ragweed extract. A group of 10 guinea pigs received repeated intracutaneous injections of the toxin ragweed extract mixture in 0.1 c.c. amounts at intervals of four days. Six injections in all were given. The usual interval of three weeks followed, and then sensitivity was tested for by intravenous injection of a ragweed extract. No greater percentage of guinea pigs was sensitized by the use of ragweed extract staphylococcus toxin than by the ragweed extract alone.

Harrison[3] used alum-precipitated ragweed pollen in the hope that "slow absorption of the precipitated extract would permit the injection of larger amounts in fewer doses and at greater intervals." Alum-precipitated ragweed extracts were used to desensitize guinea pigs

*Connaught Laboratories and Department of Physiology, University of Toronto.

previously sensitized by injection with an aqueous extract of ragweed pollen. Thus most of Harrison's report had to do with desensitization using alum-precipitated ragweed extract. In a group of 10 guinea pigs, half of which were sensitized with aqueous extract and half sensitized with alum-precipitated ragweed extract, Harrison noted the latter group was more sensitized. Thus, in the group sensitized with the alum-precipitated extract three showed severe symptoms, one dying in three minutes; whereas in the group sensitized with aqueous extract, two only showed mild symptoms. Harrison concluded that alum-precipitated ragweed pollen extract is a very effective sensitizing agent in guinea pigs.

Harrison[3] states that it has been shown that guinea pigs may be readily sensitized by the injection of extracts prepared from various plant pollens. This had not been our experience with ragweed pollen extracts as outlined above, and the results obtained by Harrison with the use of alum encouraged us to use our watery extract of ragweed pollen precipitated with alum.

PREPARATION OF RAGWEED EXTRACT ALUM PRECIPITATED

The watery extract of ragweed pollen used for precipitation with alum was prepared in the same manner as when used without alum. Briefly this was prepared as follows.

The ragweed pollen was defatted with ether, ground in a ball-mill for eight hours, and extracted with 20 parts of distilled water. The pollen extract was rendered sterile by passing it through a Seitz filter. A 10 per cent solution of potassium alum ($Al_2[SO_4]_3K_2SO_4\,24H_2O$) was added to the pollen extract to give a final concentration of 1 per cent potassium alum.* A slight flocculent precipitate resulted on adding the potassium alum to the ragweed extract. The ragweed extract alum precipitated was allowed to stand twenty-four hours and was shaken well before injecting the guinea pigs.

SENSITIZATION OF GUINEA PIGS

On two successive days a group of five guinea pigs, designated A, was given subcutaneously 1 c.c. of the ragweed extract alum precipitated. A second group of five guinea pigs, designated B, was given 5 c.c. subcutaneously of the ragweed extract alum precipitated. An interval of eight weeks followed. One guinea pig was selected from Group A and was given 0.5 c.c. intravenously of a 5 per cent watery extract of ragweed (W.E.). The guinea pig developed marked anaphylactic shock from which it recovered. Two guinea pigs were selected from Group B and given 0.5 c.c. of a 5 per cent watery extract of ragweed intravenously. Both guinea pigs died of typical anaphylactic shock which was confirmed by postmortem findings. One week later a guinea pig was selected from

*The alum solution should be rendered sterile by passing it through a Berkefeld candle and then added to the ragweed extract with sterile precautions.

each of the above two groups and each received 0.75 c.c. of 5 per cent ragweed extract intravenously. Both guinea pigs died of typical anaphylactic shock. Ten days later, or ten weeks after the initial injection, a guinea pig from Group B was given 0.05 c.c. intravenously of the 5 per cent ragweed extract and died of typical anaphylactic shock. Table I is a summary of the results obtained.

TABLE I

GUINEA PIGS INJECTED WITH RAGWEED EXTRACT ALUM PRECIPITATED 3/4/35

INTERVAL	METHOD OF SENSITIZATION		SHOCKING DOSE (INTRAVENOUSLY)
	GROUP A 1 C.C. SUBCUTANEOUSLY 2 SUCCESSIVE DAYS	GROUP B 5 C.C. SUBCUTANEOUSLY	
	5 guinea pigs	5 guinea pigs	
57 days	1 guinea pig, marked shock, recovered	2 guinea pigs died of anaphylactic shock	0.5 c.c. W.E.*
64 days	1 guinea pig died of anaphylactic shock	1 guinea pig died of anaphylactic shock	0.75 c.c. W.E.
74 days		1 guinea pig died of anaphylactic shock	0.05 c.c. W.E.
108 days	1 guinea pig, marked shock, recovered		0.5 c.c. W.E.
	2 died of intercurrent infection	1 died of intercurrent infection	

*W.E. = watery extract ragweed pollen.[1]

Another group of 30 guinea pigs received subcutaneously 2.5 c.c. of ragweed extract alum precipitated on August 22, 1935. Two months later four of these guinea pigs were selected, and each received 0.4 c.c. of 5 per cent ragweed extract intravenously, and all died of typical anaphylactic shock. One week later four more guinea pigs of this group were selected, and each received 0.5 c.c. of 5 per cent ragweed extract intravenously. Three of this group died of anaphylactic shock, and one had a very marked anaphylactic reaction but recovered. One day later two more of this group were reinjected as above, and one guinea pig died of anaphylactic shock and the other had a very marked reaction but recovered. In this group of ten guinea pigs which were reinjected, eight died of anaphylactic shock and two had very marked reactions but recovered. The remainder of this group was reserved for use in another type of experiment which will be reported later. Table II is a summary of the results obtained.

TABLE II

GUINEA PIGS SENSITIZED WITH RAGWEED EXTRACT ALUM PRECIPITATED 8/22/35

INTERVAL	METHOD OF SENSITIZATION 2.5 C.C. SUBCUTANEOUSLY	SHOCKING DOSE (INTRAVENOUSLY)
60 days	4 guinea pigs, all died	0.4 c.c. W.E.*
68 days	3 guinea pigs died; 1 guinea pig marked shock, but recovered	0.5 c.c. W.E.
69 days	1 guinea pig died; 1 guinea pig marked shock, but recovered	0.5 c.c. W.E.

*W.E. = watery extract of ragweed pollen.[1]

The foregoing results using alum as an adjuvant show the constancy with which guinea pigs can be sensitized as judged by anaphylactic death, and is to be contrasted with the poor results obtained with the 54 guinea pigs cited in the earlier part of this paper.

The exact explanation of this finding has not been ascertained. Harrison[4] has demonstrated that with alum-precipitated diphtheria toxoid the delay in absorption is considerable, lasting up to the seventh week. It is possible that alum delays the absorption of the pollen extract as it does with diphtheria toxoid, and in this way the stimulus persists over a longer period and thus induces greater sensitivity than when alum is not present. This parallelism, if correct, affords something of interest in that alum will act with an antigen producing immunity and also with an antigen to increase sensitivity or induce in an animal a definite anaphylactic state.

SUMMARY

The addition of alum to ragweed extract makes it possible to sensitize a very high percentage of guinea pigs to ragweed pollen extract.

REFERENCES

1. Caulfeild, A. H., Brown, M. H., and Waters, E. T.: Experiments to Determine Whether the Allergically Active Substance in Ragweed Pollen Extract Is a Single Entity or Multiple, J. ALLERGY 7: 1, 1935.
2. Burky, Earl L.: The Production in the Rabbit of Hypersensitive Reactions to Lens, Rabbit Muscle and Low Ragweed Extracts by the Action of Staphylococcus Toxin, J. ALLERGY 5: 466, 1934.
3. Harrison, W. T.: Public Health Reports, U. S. Treasury 49: Part 1, p. 462, 1934.
4. Harrison, W. T.: Some Observations on the Use of Alum Precipitated Diphtheria Toxoid, Am. J. Pub. Health 25: 298, 1935.

HYPERSENSITIVENESS TO FUNGI

GRAFTON TYLER BROWN, B.S., M.D.
WASHINGTON, D. C.

IT IS fairly common knowledge now that bronchial asthma, hay fever, eczema, urticaria, and other allergic diseases are usually due to sensitization to pollens, animal epidermals, foods, bacteria, drugs, or various air-borne substances such as house dust, orris root, and silk. The purpose of this paper is to call attention to the fact that such related allergic conditions may likewise be due to sensitization to common molds and yeasts.

The potentiality of molds being air-borne may be appreciated if we compare the size of the ubiquitous spores with the size of pollen grains. The microphotographs in Figs. 1 and 2 show the relative size of mold spores and pollen grains. The average diameter of mold spores is from 3 to 5 microns; whereas the diameter of the common air-borne pollen grains is from 15 to 40 microns. It has been reported that aviators have found plant disease spores at altitudes of 18,000 feet. Most of the spores gathered at high altitudes were from fungi known to attack small grains and vegetables. Many fungi discharge enormous numbers of spores into the air; and these, being very light, are carried many hundreds of miles. One mushroom may discharge as many as 18 billion spores.

Microorganisms may be divided into four distinct groups: the *Schizomycetes* or bacteria, the *Hyphomycetes* or molds, the *Blastomycetes* or yeasts, and the protozoa. The bacteria, molds, and yeasts belong to the plant kingdom; whereas the protozoa belong to the animal kingdom. The molds have been classified into five families, with several hundred genera and thousands of different species. From the standpoint of allergy, this is a vast and relatively unexplored field. I have selected for study those varieties which have already been reported by other investigators, and also all the different fungi (molds and yeasts) that could be cultured from patients' skin lesions, sputum, stools, and environmental (house and mattress) dusts. Fungi, in addition to molds and yeasts, include rusts, smuts, mushrooms, etc.

REVIEW OF LITERATURE

The late Professor Storm van Leeuwen[1] had a clear claim to priority in the matter of asthma due to sensitization to molds, as he was the first to call attention to the importance of mold allergens in the causation of this disease. He[2] attributed the climatic type of asthma, so prevalent in Holland, to products of the growth of molds, yeasts, or bacteria, which

he termed "climate allergens or miasms." Storm van Leeuwen[3] usually worked with six different molds: *Aspergillus flavus, Aspergillus fumigatus, Aspergillus nidulans, Aspergillus niger, Mucor,* and *Penicillium.* By testing his asthmatic patients intracutaneously with extracts of these molds, he found about 50 per cent of them sensitive to mold allergens.[4] He also found about 20 per cent of his asthma patients sensitive to an allergen formed in grain infested with common mites.

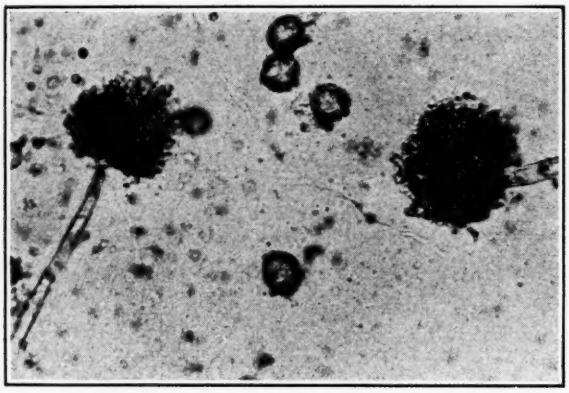

Fig. 1.—Aspergillus heads with ragweed pollen grains for comparison of size. Note the minute spores contained within the heads. (Prince et al., Texas State J. Med.)

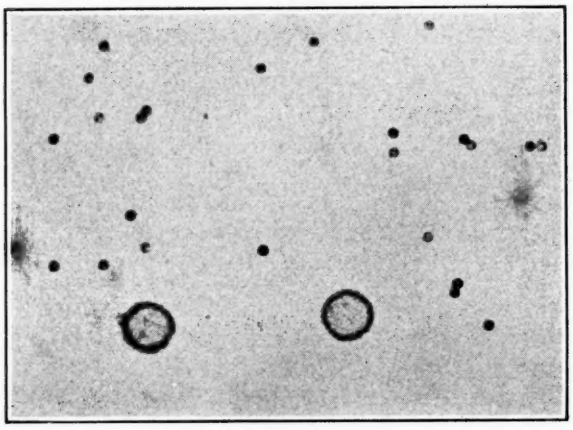

Fig. 2.—Individual spores and ragweed pollen grains. Note the comparative size. (Prince et al., Texas State J. Med.)

Cadham[5] reported three instances of asthma due to sensitization to grain rusts. Although Cadham's article was a very brief one, he was the first to call attention to cases of asthma due to inhalation of the spores of fungi, but he made no reference to sensitization to the common dust molds.

Hansen[6] in Germany found that 15 per cent of his asthma patients gave positive skin reactions to one or more of the following molds: *Aspergillus fumigatus, Aspergillus glaucus, Aspergillus nidulans, Asper-*

gillus niger, and *Penicillium glaucum.* He was able to reproduce asthmatic attacks in a number of these patients by having them inhale spores of the reacting molds.

Hopkins, Benham, and Kesten[7] were the first in the United States to report a case of asthma due to a mold (*Alternaria*). Their patient, in addition to being markedly sensitive to *Alternaria,* gave definitely positive skin reactions to several other molds, including *Aspergillus nidulans* cultured from an eczematous lesion on his leg.[8] In this connection it may be stated that some years previously, Hilgermann[9] and Niethe[10] had attributed certain cases of eczema to sensitization to common saprophytic molds which grew on the skin lesions.

Gehlen and Otto[11] observed that many of their patients with asthma also had rheumatic symptoms, and that most of them gave positive reactions to cutaneous tests with molds. After testing 125 such patients, most of whom lived in damp houses, they concluded that there was an etiologic relationship between asthma and rheumatism, and that sensitization to molds was of some significance in the pathogenesis of these diseases.

Bernton[12] described a patient with asthma due to a mold—*Aspergillus fumigatus.* Specific treatment was attempted in this case but was discontinued after the third subcutaneous injection of a 1:5,000 extract of *Aspergillus fumigatus,* because of the severe asthma produced by these injections. These constitutional reactions served to confirm the diagnosis.

Ramirez and Eller[13] reported two cases of contact dermatitis (dermatitis venenata), and one case of asthma and urticaria, due to sensitization to green *Penicillium.*

Medical literature contains numerous references to Trichophytin hypersensitiveness in persons with deep-seated ringworm infections; and Low[14] and Bloch[15] have reviewed the subject in detail. Later on, Jadassohn and Peck[16] showed that this skin hypersensitiveness to Trichophytin was also quite constantly present in superficial tinea infections. Sulzberger and Lewis,[17] by means of contact or patch tests with Trichophytin, demonstrated that products of fungi were capable of causing an eczematous eruption on a hypersensitive skin. Ramirez[18] has reported a case of hay fever and asthma which could be traced to Trichophytin sensitization.

Sulzberger and Kerr[19] recorded the case of a man with tinea of the hands and feet, who gave immediate, marked, urticarial-wheal reactions to intradermal Trichophytin tests. With this patient's blood serum, they were able, by passive transfer of the urticarial Trichophytin hypersensitiveness to the skin of normal nonsensitive individuals, to demonstrate the presence in the blood of Prausnitz-Küstner antibodies or specific reagins. Wise and Sulzberger[20] reported the case of a patient with dermatitis, and occasional attacks of urticaria, asthma, and hay

fever, in whom an intradermal test with Trichophytin produced an acute attack of hay fever and generalized hives, necessitating the administration of epinephrine for relief.

Flood[21] has reported the case of one patient with asthma due to sensitivity to *Mucor plumbeus*. He also stated that in a group of 55 patients with chronic asthma, 14 per cent gave positive skin reactions to common dust fungi.

Balyeat and his coworkers,[22] after considering the high mold content of the air in comparison with the pollen count and the fact that less than 1 per cent of their patients tested with various molds gave definite reactions to them, concluded that patients do not become sensitive to molds with the same ease that they do to pollens. Their study indicated that in Oklahoma molds do not occupy a prominent position in the etiology of asthma or rhinitis. They found, however, that sensitization to molds appeared to be a definite factor in the production of asthma and rhinitis in occasional cases and must always be kept in mind as a possible primary or secondary factor in both asthma and rhinitis in any section of the United States.

Cobe[23] reported the case of a patient with asthma due to hypersensitivity to *Cladosporium fulvum*, a mold appearing on the leaves of tomato plants. Marked improvement and relief occurred through desensitization with an extract made from the mold infesting the tomato plants. A similar case was reported to me by Dr. Herbert K. Detweiler[24] of Toronto. Dr. Detweiler's patient grew tomatoes under glass, and harvested them twice a year, that is, in June and December, at which times he always had attacks of asthma. These tomato plants were nearly always heavily contaminated with *Cladosporium fulvum*. This patient was sensitive to the *Cladosporium fulvum*, but not to the tomato plant, flower, or fruit, or anything else with which he was tested.

Jimenez-Diaz and his coworkers,[25] in a paper on climatic asthma, stated that climate strongly influences the appearance of attacks in a very high percentage of asthmatic persons. Sometimes it does this through various nonspecific influences, and at other times the existence of true allergens peculiar to climate is the direct cause of attacks. They concluded that true cases of climatic asthma in Spain were nearly always coastal, and were due to the existence of abundant fungi in the air and in household articles in those places. Studies of the etiologic rôle of fungi were reported. The fungi principally responsible for attacks were *Aspergillus, Mucor, Penicillium*, and, to a lesser degree, certain clamidoes. These studies on fungi considered their cultivation from the air, specific skin tests, passive transfer, provocation of attacks by introduction of fungi in the patient's environment, and the demonstration of the hemoclastic reaction.

Towey and his coworkers[26] in Michigan carried out a study on a series of 35 patients whose symptoms were acute and typically asthmatic.

On investigation it was found that these patients were working where they came in contact with dust from maple logs that had been cut for more than a year. The dust proved to be spores of a fungus, identified as *Coniosporium corticola*. Extracts of the spores produced local skin reactions in the affected group, as did also a suspension of macerated spores, while control tests were negative.

Taub[27] reported a case of asthma in a five-year-old boy with a four-plus reaction to yeast by scratch and intracutaneous tests. Passive transfer was done, with markedly positive reactions to yeast protein. Omission of yeast products from the diet stopped the asthma, which had been present for two and a half years. Desensitization to yeast was attempted by the subcutaneous method.

Bernton and Thom[28] described the clinical features of two groups of patients, each containing four in number and presenting different types of vasomotor rhinitis. Cutaneous and subcutaneous tests indicated sensitiveness of the patients to molds. Of the mold preparations used in testing, *Alternaria* and Trichophyton were found to be the only two causing symptoms in these patients. *Alternaria* is commonly found in dust. Trichophyton is a common parasite of the integument of man, and thus human contacts may provide allergenic material. Gratifying results were obtained by specific desensitization with the appropriate mold extracts. The distinction between sensitiveness to molds and infection with molds was emphasized by these authors.

Ellis[29] reported that during damp weather in Port Sudan, which is situated on the western shores of the Red Sea, molds occurred profusely in the atmosphere, and asthma was common. Skin tests showed that these molds had a specially selective influence on asthmatic subjects, and specific mold desensitization resulted in improvement of the asthma.

Prince and his coworkers[30] found that molds of various kinds were unusually prevalent, in both the outside and the inside air of Galveston, Texas. Certain cases of asthma and hay fever in that vicinity seemed to be related in some way to north winds, which were heavily laden with molds. Strongly positive skin tests to mold extracts indicated definitely that molds were causative agents in some cases of asthma and hay fever. Their results with mold therapy were distinctly encouraging.

CULTURE, ISOLATION, AND IDENTIFICATION OF FUNGI

Dusts from various sources, principally house and mattress dusts, were cultured on Czapek's solution agar, dextrose agar, and Sabouraud's medium in pour plates. The plates were then incubated at 37.5° C. and at room temperature for three to seven days. These plates were observed daily during this time for evidences of growth, and the characteristics of all colonies were studied. Daily observations were absolutely essential because of the profuse growth which sometimes occurs in a relatively

short time, making it difficult, if not impossible, to isolate in pure culture the various molds, yeasts, and bacteria, unless subcultures and subsequent plates are made.

As soon as the individual colonies made their appearance, they were fished and subcultured on slants of Czapek's solution agar, 1 per cent dextrose agar, Sabouraud's medium, or such other media as were indicated by the morphology of the colony and the characteristics of the organism. These subcultures were then incubated at 37.5° C. and at room temperature until the typical, colored hyphae developed, during which time daily observations were made as to the progress and characteristics of the growth. Complete coloration of the aerial hyphae developed usually in from one to seven days, depending to some extent on the character and type of the mold. During this time, microscopic preparations were examined, and notations made of the method of development of the stalk, conidiophores, spores, etc., of the individual molds.

After coloration was complete, final observations were made macroscopically and microscopically and, in many instances, special fermentation tests and biologic determinations were also made. These findings, together with previous observations, were compared with known mold cultures. These observations and comparisons, together with reference to the works of Buchanan and Buchanan,[31] Thom and Church,[32] and Guilliermond and Tanner,[33] were sufficient in most instances to identify the mold or yeast in question, but in other instances it was possible to report the mold or yeast only as belonging to a certain group, and not as a specific entity.

The principal media used were Czapek's solution agar, 1 per cent dextrose agar, Sabouraud's medium, and 2 per cent maltose broth. These media are especially suitable for the growth of molds and yeasts. In addition to these, other special media peculiarly adaptable to certain types of growth were used; and of course, the routine media for the growth and differentiation of the various bacteria were also used in the work of cultivation, isolation, and identification.

PREPARATION OF DIAGNOSTIC AND THERAPEUTIC MATERIALS

Powders and Filtrates.—The molds from which powders and filtrates were to be made were inoculated into malt extract broth. These cultures were allowed to stand at room temperature for twenty-five to thirty days, during which time a definite and specific felt developed on the surface of the media. After growing for this length of time, the mixture of felt and broth was paper filtered, and the broth filtrate was caught in a sterile container. The felt, which remained on the filter paper, was dried in the incubator for forty-eight hours. It was then transferred to a sterile mortar and ground into a fine powder, which was placed in a sterile tube and labeled. In some instances, when the felt did not dry

after a period of forty-eight hours in the incubator, it was necessary to freeze it with dry ice and grind the felt in this condition.

The broth filtrate was again filtered, this time through a Berkefeld candle or a Seitz filter. This filtrate was then transferred to a sterile vaccine vial, and cultured for sterility, both aerobically and anaerobically, for at least seventy-two hours, after which it was refrigerated and ready for use.

The medium used for growing molds for this purpose consisted of a 10 per cent solution of malt extract in distilled water. This medium seemed to be superior to other preparations for the development of a massive felt and a potent filtrate. The yeasts were cultured in a manner similar to that used for molds and for bacteria. The types of media most suitable for the growth of yeasts are sugar broths and beer wort, with or without the addition of agar or gelatin.

Glycerin Extracts.—Concentrated (2 to 10 per cent) glycerin extracts of the various fungi were also prepared, in addition to the dried powdered felts and sterile broth filtrates just referred to. The 2 per cent glycerin extracts were prepared by adding one gram of the dried powdered felt to 50 c.c. of an extracting fluid, consisting of 50 per cent glycerin and 50 per cent buffered salt solution. Sterile glass beads were added to facilitate shaking, and prevent clumping. The buffered salt solution in the extracting fluid was made by adding 2.7 grams of sodium bicarbonate and 5 grams of sodium chloride to 1,000 c.c. of distilled water. These mold extracts were refrigerated for a week, and thoroughly shaken at least once daily. The extracts were then filtered through a Berkefeld candle or a Seitz filter, and examined for sterility. Ten per cent mold extracts are naturally more potent than the 2 per cent extracts, and are therefore preferable when sufficient dried felt is available.

Trichophytin.—Trichophytin was prepared somewhat after the method described by Sulzberger,[34] which was Bloch's modification of the original Plato-Neisser technic. One hundred cubic centimeters of dextrose broth (Difco) containing 3 grams of beef extract, 5 grams of peptone, and 5 grams of dextrose, were placed in a 1,000 c.c. Erlenmeyer flask. The malt extract broth which was so satisfactory for massive growth of the parasitic molds was found to be unsuitable for growing *Trichophyton*. As Dr. Thom pointed out that pathogenic fungi grow best on media containing some animal extract, the dextrose broth was substituted for the malt extract. The flask and contents were then sterilized in an autoclave for twenty minutes at 15 pounds pressure (250° F.). A plant was made from a vigorously growing, several weeks' old culture of *Trichophyton gypseum*. After an interval of at least three months, the cultures, which had grown in a thick layer on the surface of the broth, were removed and placed in a sterile mortar, and thoroughly triturated with dry ice and kieselguhr. During trituration a sufficient quantity of the

culture broth was added to produce a thin gruel-like mush. This liquid eventually contained about one-half the original quantity of broth. One-half of 1 per cent phenol was then added as a preservative. The fluid was shaken thoroughly for about an hour, and thereupon placed in an incubator for twenty-four hours. Upon removal, the remainder of the culture broth was added, and it was again thoroughly shaken for about an hour. After this the preparation was filtered through a sterile Seitz filter. The filtrate was tested for sterility upon usual culture media, filled into sterile vaccine vials, and was then ready for use.

TESTING AND TREATING WITH FUNGI

A considerable number of patients with asthma, eczema, perennial hay fever, and other related conditions have been tested more or less routinely for sensitization to fungi. The cutaneous or scratch method has been used almost exclusively, but in a few selected cases the intradermal method of testing has also been used.

The crude molds growing on Sabouraud's or Czapek's media may be used for cutaneous testing, but they are somewhat difficult to handle. The principal objection, however, to the use of crude molds for diagnostic skin tests is that the spores get in the air and contaminate almost everything in the office or clinic in which they are being handled. Furthermore, the pathogenic fungi, such as *Trichophyton,* should not be tested in this form because of the likelihood of producing a localized infection. On two occasions, I inadvertently produced a troublesome skin ulcer by using a viable culture of *Sporotrichum schenckii* for cutaneous testing.

The dried powdered felt makes satisfactory material for the scratch test and is dissolved on the skin with tenth-normal sodium hydroxide solution, just as in tests with other dried protein preparations. The same objection, however, applies to the use of the dried felt for test purposes, as to the use of crude molds, namely, the likelihood of contamination from viable spores.

The sterile broth filtrates may be used undiluted for cutaneous testing, diluted ten times with phenolized salt solution for intradermal testing, and in weaker dilutions for treatment purposes. As these filtrates, however, consist of nutrient broth without any preservative, they are quite easily contaminated, and therefore must be handled with strict aseptic precautions. If the filtrates are to be used for test or treatment purposes, it is safer to add 0.5 per cent phenol as a preservative, although even this precaution will not always prevent contamination. For treatment purposes, 1:10, 1:100, and 1:1,000 dilutions of the broth filtrates should be prepared with sterile normal salt solution containing 0.5 per cent phenol.

The concentrated glycerin extracts previously referred to are potent and stable, and perfectly satisfactory for cutaneous testing, but because of the high content of glycerin are suitable for intradermal testing only

when diluted ten times with sterile buffered salt solution containing 0.5 per cent phenol. In preparing dilutions of the glycerin extracts for treatment purposes, however, the glycerosaline extracting fluid should be used as diluent to maintain the potency and sterility of these dilutions.

Testing with all the different fungi on hand required over 70 separate skin tests; so after considerable work with the fungi, all the different species of each genus were mixed together, to shorten and simplify the testing procedure. For example, an *Alternaria* mixture was prepared containing equal quantities of *Alternaria humicola* and *Alternaria mali* glycerin extracts; an *Aspergillus* mixture was made with equal parts of each of 16 different species of *Aspergilli;* a *Mucor* mixture consisted of equal parts of each of nine different *Mucor* glycerin extracts, and so on. Whenever a patient reacted to one of these mixtures, the individual species composing that mixture were then tested.

In testing with the various preparations of the fungi, suitable controls should be used, namely, tenth-normal sodium hydroxide for the crude molds and the dried powders, sterile phenolized malt extract broth for the broth filtrates, the glycerosaline extracting fluid for the glycerin extracts, and phenolized dextrose broth for the Trichophytin.

CLINICAL DATA

I have encountered 20 patients who gave definite, immediate, urticarial-wheal reactions to one or more fungi on cutaneous tests. This does not take into consideration a much larger number of patients who gave only slight or doubtful, or delayed reactions, or who reacted to fungi only when tested intradermally. The 20 patients who were definitely sensitive to fungi varied in age from one to forty-four years, and the sexes were about equally divided. Nine of this group were chronic asthmatic patients, five were afflicted with bad eczema, two others suffered from asthma and eczema together, one had hay fever and mucous colitis, another had vasomotor rhinitis, one complained of vasomotor rhinitis and "rheumatism," and the remaining patient sought relief from chronic bronchorrhea and hyperhidrosis of hands and feet.

The following points gleaned from the histories of these patients suggested sensitization to molds: asthma and nasal symptoms were aggravated by damp, musty places such as cellars, old farmhouses, boat cabins, and caverns; symptoms were also worse at the seashore and in damp, rainy weather; patients were practically or entirely free from asthma or sneezing for months at a time while staying in certain dry places; trouble disappeared in the mountains but recurred promptly when patients returned to sea level; asthma and nasal trouble were definitely worse in summer and better in cold, dry weather; attacks were worse indoors than out, usually coming on at night, either shortly after retiring or in the early morning hours; patients were better at school or office than at home, and while away visiting might be entirely free from symptoms;

eczema, when present, was practically limited to exposed parts of the body, namely, the face, neck, and arms; practically all these patients complained that dust affected them, that is, produced itching of the eyes, sneezing, running of the nose, wheezing, coughing, or even skin irritation. Most of the above points are readily understood when we consider that moisture, darkness, and warmth favor the growth of molds.

The patients under discussion reacted to from one to twenty of the following fungi: *Alternaria humicola, A. mali, A. sp., Aspergillus candidus, A. clavatus, A. conicus, A. flavipes, A. fumigatus, A. glaucus, A. hortai, A. nidulans, A. niger, A. oryzae, A. parasiticus, A. terreus, Cephalothecium roseum, Citromyces sp., Dicoccum asperum, Epidermophyton inguinale, Monilia sitophila, M. sp., Mucor mucedo, M. plumbeus, Penicillium chlorophaeum, P. chrysogenum, P. cyclopium, P. elongatum, P. expansum, P. italicum, P. lanosum, P. roqueforti, P. sp.* (green), *Saccharomyces cerevisiae, Trichophyton gypseum,* grain smut, mushroom, yeast (bakers and brewers). A number of these will be recognized as newcomers to be added to the already lengthy list of allergens.

In my experience, ordinary yeast, *Saccharomyces cerevisiae,* is the most frequent offender among the fungi, having reacted in 12 of the 20 cases, or 60 per cent of the fungus sensitive patients. *Alternaria* is second in importance of the various fungi studied, and the most frequent reactor among the molds, having reacted definitely in six patients, or 30 per cent of the fungus cases. The third place of importance was shared by *Aspergillus fumigatus* and edible mushroom, each reacting in four cases, or 20 per cent of the fungus sensitive patients.

It is interesting to note that one patient's asthma was definitely aggravated by inhalation of some of the spores, incident to skin testing him with crude molds and dried felt preparations, and it was necessary to take the precaution of tying a folded handkerchief over his nose and mouth while the dry mold preparations were being handled in his presence. Reference has already been made to the disadvantages of testing with crude molds and dried powdered felt.

Passive transfer, according to the method first described by Prausnitz and Küstner,[35] was attempted in only two of the mold sensitive patients but was successful in both. In other words, with the patients' blood serum, the specific mold sensitization (*Alternaria* in one case, *Penicillium* in the other) was transferred locally to the skin of a normal non-sensitive individual. This demonstrated conclusively that the blood of these patients contained specific reacting bodies, known as atopic reagins.

The method of treating hypersensitiveness to molds and yeasts is essentially the same as that used for other types of allergenic substances. Yeast and mushroom in all forms were completely eliminated from the diets of those patients who reacted to these edible fungi. All possible dust precautions were ordered for the mold sensitive patients. The bedrooms and living quarters of these patients were thoroughly

cleaned and kept as free from dust as possible by frequent vacuuming. All unnecessary dust catchers, such as nonwashable rugs and draperies, were removed. Mattresses and pillows were covered with dust proof casings. Very satisfactory covers can now be purchased for mattresses, box springs, and pillows. These are made to measure at quite low cost, are impervious to dust, and can be sewn or zippered on. Intensive local treatment was advised for epidermophytosis when accompanied by *Trichophyton* sensitization. Desensitizing injections with extracts or filtrates of the specific reacting fungi were resorted to in a number of the cases, with very satisfactory results. No unpleasant constitutional reactions followed any of the hyposensitizing doses, although a transitory aggravation of symptoms occurred in a few instances. Although the above mentioned dust precautions were advised in most cases, some of the dust sensitive patients have done well on the specific hyposensitizing injections, without making any special changes in their environment.

THE HOUSE DUST PROBLEM

Ever since Cooke[36] first called attention to the presence in most house dusts of a specific substance that is in itself an important etiologic factor in bronchial asthma, allergists have been seeking in vain to discover the exact nature and source of this reacting substance.

Rowe[37] contended that house dust reactions depended on one or more environmental substances, such as animal emanations, orris root, pollens, and various fabric dusts, and that the possibility of an unknown specific substance in house dust was unlikely. This contention has been repeatedly refuted, however, by the fact that most of the house dust sensitive individuals react either exclusively or dominantly to house dust extracts.

Dr. Thom has wisely said that "the *Penicillia*, the *Aspergilli*, and the *Mucors* are the weeds of the culture room." I would add that molds are also the weeds of the home. Every specimen of house or mattress dust that has been cultured was found to contain various fungi. Molds, therefore, must be given consideration in any study of the house dust problem.

Cohen[38] reported 19 cases of asthma due to dusts from mattresses. These patients gave large reactions to extracts of the dust collected from their own mattresses but did not react to cotton or kapok, of which the mattresses were made. In each instance complete relief was produced almost magically by discarding the offending mattress and substituting a new one. In three cases, however, attacks recurred after free intervals of from four to six months, whereupon positive skin tests were again obtained to extracts of the new mattresses. It was found that these recurrences could be prevented by covering the mattresses with some impervious material, such as rubber sheeting or satin fabrikoid. Cohen thought it probable that mattresses became infested with molds to

which patients became sensitized, as had been previously pointed out by Storm van Leeuwen.[39] This theory was substantiated by the fact that the mattresses when new produced no symptoms in patients, and dust extracts from them gave no reactions; yet after several months' use these same mattresses caused trouble, and their dusts then reacted.

Early in my work with molds I too concluded that the allergenic substances in house dust, other than the well-known air-borne allergens, consisted of mold spores. This opinion was strengthened by the following case. A boy with asthma and perennial hay fever was brought to me, and he gave positive reactions to skin tests with extracts of his own house dust, as well as to dust obtained from a house at the seashore where he had particularly bad asthma. Cultures from his own house dust and from the seashore house dust revealed *Alternaria* as the predominating mold. Skin tests with all available molds, both stock and autogenous, were negative except for definitely positive reactions to stock and autogenous *Alternaria* preparations. The *Alternaria* reactions exceeded those obtained with the whole dust extracts. It seemed quite evident, therefore, that this patient's asthma and hay fever symptoms were due to sensitization to a mold *(Alternaria)* contained in the house dust. Unfortunately, however, other extensive researches showed this case to be a rare exception rather than the rule.

Because of the importance of the house dust problem, it would seem worth while to discuss briefly the results of my studies on dust sensitization. Generally speaking, mattress dust was found to be more reactive than house dust. From the fact that in some instances a definitely positive reaction was obtained to a scratch test with a very small quantity of the dry dust itself, it may be assumed that the reacting substance was generally distributed throughout the dust. That the dust reactions were due to a specific sensitization, and not merely to a nonspecific irritation or histamine reaction, was proved by the fact that these same dusts failed to react when they were tested on the skin of other persons, both allergic and nonallergic. Skin tests with epidermals, pollens, orris root, and other air-borne substances failed to show a reaction that would in any way account for the allergenic properties of the house and mattress dusts. Patients definitely sensitive to extracts of their own cotton felt mattress dust gave no reaction whatever to cotton or cottonseed; likewise, individuals showing definite, positive reactions to scratch tests with extracts of their own kapok mattress dust were not sensitive to kapok or kapok seed.

Some of the sensitizations to dust (chiefly mattress dust) have a definite specificity, as scratch tests with dust extracts from various other sources were all negative. It seemed, therefore, that these specific dust sensitizations were probably due to fungi which were present in the mattress or house dusts. Scratch tests with a large number of stock mold preparations, however, were completely negative. It is true that

on intradermal tests, a number of positive reactions were obtained with sterile broth filtrates and extracts of various molds, some of these reactions being immediate and some delayed. However, as it was necessary to inject these mold preparations intradermally to obtain positive reactions, none of them explained the immediate, urticarial reactions to scratch tests with the house and mattress dusts.

Dust sensitive patients were scratch tested with all the various fungi and bacteria that could be cultured from their reacting house or mattress dusts, but with completely negative results other than an occasional slight or doubtful reaction which did not explain the definite dust sensitivity. Cultures from different specimens of dust from the same mattress at times revealed entirely different fungi, none of which explained the sensitivity to the dust itself. This shows the multiplicity of molds present in dust and the difficulty in locating the offending one by the culture method. If the reacting substance in dust consists of spores of some fungus (the most probable explanation), the failure to find this fungus may have been due to the fact that the spores were nonviable from age and drying, which would not interfere with their allergenic properties, but would prevent their growth when transferred to culture media. Bacteria very rarely give immediate skin reactions, so it was not thought likely that the reacting substance in the dusts would be any of the bacteria found, and therefore it was not surprising when they failed to react.

Because of the possibility that the reactivity of house or mattress dust might be due to some symbiotic allergen, a separate flask was inoculated with all the fungi and bacteria cultured from each specimen of dust, and dried felt and sterile broth filtrates were prepared from these mixtures. No reactions were obtained, however, to skin tests with these symbiotic preparations. Separate flasks were then inoculated with all the fungi isolated from each specimen of cotton felt mattress dust, and to these flasks were added some sterile cotton fiber and cottonseed meal, to reproduce, as nearly as possible, the conditions within the cotton mattresses; similarly, flasks were inoculated with all the fungi and bacteria isolated from kapok mattress dust, to which were added some sterile kapok fiber and kapok seed meal. Dried felt and broth filtrates were prepared from each of these cotton or kapok treated symbiotic flasks, but when tested on the particular patients these preparations also failed to react.

As it was thought that the fungi and other organisms might have produced the allergenic substance present in mattress dust, by some action on the cottonseed or kapok seed protein within the mattresses, a batch of cottonseed meal was moistened with water and inoculated with all the microorganisms isolated from a specimen of cotton felt mattress dust; likewise, some moistened kapok seed meal was inoculated with all the fungi and bacteria from kapok mattress dust. After these mixtures had stood for about a month, being remoistened when necessary to pro-

mote free growth of the fungi, the masses were dried, and tested on the particular patients, but with the same disappointing results. The reacting substance in mattress dust was still an unknown quantity.

Similar researches were conducted on a considerable number of dust sensitive patients, but in only an occasional case was it possible to incriminate any mold or other known allergen as the reacting substance in the dust.

Recently Cohen, Nelson and Reinarz[40] reported that fresh cotton linters sealed air-tight in a jar and autoclaved for one hour at a temperature (120° C.) believed to be high enough to kill all molds and bacteria, and then kept for some months, developed the same allergenic property as was possessed by house dust. They concluded from this that the reacting substance in house dust was some degenerative product of cotton linters developed during the aging process.

SUMMARY

This paper gives the results of an intensive study of human hypersensitiveness to fungi, including a comprehensive review of the literature, and a discussion of the house dust problem with particular reference to molds.

The method of diagnosing and treating hypersensitiveness to molds and yeasts is essentially the same as that used for other types of allergenic substances.

Sensitization to fungi must take its place along with sensitization to pollens, animal epidermals, foods, and bacteria in the causation of bronchial asthma, eczema, perennial hay fever, and other related allergic conditions.

The numerous fungi used in my work have been obtained from various sources. Quite a number of mold cultures were sent to me from the Laboratory for Medical Mycology of Columbia University College of Physicians and Surgeons, New York, through the courtesy of Drs. Hopkins and Kesten of the Department of Dermatology, and Chester W. Emmons, Associate in Mycology. Some of the mold preparations were furnished by Dr. Charles Thom, Principal Mycologist of the U. S. Department of Agriculture. Dr. Thom also identified some of the molds for me. The late Dr. Storm van Leeuwen of Holland, kindly sent me extracts of six different molds, and also an extract of grain infested with mites. Cultures of a few molds were contributed by Dr. Oscar B. Hunter, formerly Professor of Bacteriology and Pathology at the George Washington University School of Medicine. Dr. Hunter also rendered me invaluable assistance in the culture, isolation, and identification of fungi, and in the preparation of powders and filtrates from molds. I gratefully acknowledge his whole-hearted cooperation. Dr. Tomas Cajigas also assisted me in carrying on some of the laboratory work referred to in this article. Dried preparations of several different strains of yeast were supplied by Standard Brands Incorporated, through the courtesy of Dr. R. E. Lee. Mold, yeast, and mushroom diagnostic proteins were purchased from the Arlington Chemical Company. Dr. Fred Cadham sent me some uredospores of *Puccinia graminis* (wheat rust). A vial of spores of the maple log fungus, *Coniosporium corticola*, was sent to me by Dr. John W. Towey.

1701 Eye Street, N. W.

REFERENCES

1. Storm van Leeuwen, W.: Bronchial Asthma in Relation to Climate, Proc. Roy. Soc. Med. (Sect. Therap. & Pharm.) **17:** 19, 1924.
2. Storm van Leeuwen, W.: Allergic Diseases, Philadelphia, 1925, J. B. Lippincott Co.
3. Storm van Leeuwen, W.: Personal communication.
4. Storm van Leeuwen, W.: Asthma and Tuberculosis in Relation to "Climate Allergens," Brit. M. J. **2:** 344, 1927.
5. Cadham, F. T.: Asthma Due to Grain Rusts, J. A. M. A. **83:** 27, 1924.
6. Hansen, K.: Über Schimmelpilz-Asthma, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **40:** 204, 1928.
7. Hopkins, J. G., Benham, R. W., and Kesten, B. M.: Asthma Due to a Fungus —Alternaria, J. A. M. A. **94:** 6, 1930.
8. Hopkins, J. G., Kesten, B. M., and Benham, R. W.: Sensitization to Saprophytic Fungi in a Case of Eczema, Proc. Soc. Exper. Biol. & Med. **27:** 342, 1930.
9. Hilgermann, R.: Die Therapie und Aetiologie der chronischen Hautezeme, München. med. Wchnschr. **68:** 702, 1921.
10. Niethe, U.: Die Bedeutung der gewöhnlichen Schimmelpilze für die menschliche Haut, Arch. f. Dermat. u. Syph. **152:** 358, 1926.
11. Gehlen, H., and Otto, J.: Über kongruente Allergie-erscheinungen bei Bronchialerkrankungen und Rheumatismus, Deutsche med. Wchnschr. **55:** 1964, 1929; Simultaneous Occurrence of Bronchial and Rheumatic Diseases; Significance of Allergic Factors in Both Diseases, Abst. J. A. M. A. **94:** 371, 1930.
12. Bernton, H. S.: Asthma Due to a Mold—Aspergillus Fumigatus, J. A. M. A. **95:** 189, 1930.
13. Ramirez, M. A., and Eller, J. J.: The "Patch" Test in "Contact Dermatitis" (Dermatitis Venenata), J. ALLERGY **1:** 489, 1930; Intradermal, Scratch, Indirect and Contact Tests in Dermatology, J. A. M. A. **95:** 1080, 1930.
14. Low, R. C.: Anaphylaxis and Sensitization, New York, 1925, p. 103, William Wood & Co.
15. Bloch, B.: Allgemeine und experimentelle Biologie der Dermatomykosen, III. Die Trichophytin allergie, Jadassohn's Handb. d. Haut-u. Geschlechtskr. **11:** 336, 1928.
16. Jadassohn, W., and Peck, S. M.: Epidermophytide der Hände, Arch. f. Dermat. u. Syph. **158:** 16, 1929.
17. Sulzberger, M. B., and Lewis, G. M.: Trichophytin Hypersensitiveness Demonstrated by Contact Tests; Preliminary Report, Arch. Dermat. & Syph. **22:** 410, 1930.
18. Ramirez, M. A.: Trichophytin Sensitization, Case Report, M. J. & Rec. **132:** 382, 1930.
19. Sulzberger, M. B., and Kerr, P. S.: Trichophytin Hypersensitiveness of Urticarial Type, With Circulating Antibodies and Passive Transference, J. ALLERGY **2:** 11, 1930.
20. Wise, F., and Sulzberger, M. B.: Urticaria and Hay-Fever Due to Trichophytin (Epidermophyton interdigitale), J. A. M. A. **95:** 1504, 1930.
21. Flood, C. A.: Observations on Sensitivity to Dust Fungi in Patients With Asthma, J. A. M. A. **96:** 2094, 1931.
22. Balyeat, R. M., Stemen, T. R., and Taft, C. E.: Comparative Pollen, Mold, Butterfly and Moth Emanation Content of the Air, J. ALLERGY **3:** 227, 1932.
23. Cobe, H. M.: Asthma Due to a Mold, J. ALLERGY **3:** 389, 1932.
24. Detweiler, H. K.: Personal communication.
25. Jimenez-Diaz, C., Sanchez Cuenca, B., and Puig, J.: Climatic Asthmas, J. ALLERGY **3:** 396, 1932.
26. Towey, J. W., Sweany, H. C., and Huron, W. H.: Severe Bronchial Asthma Apparently Due to Fungus Spores Found in Maple Bark, J. A. M. A. **99:** 453, 1932.
27. Taub, S. J.: Asthma Due to Yeast (by Ingestion), J. ALLERGY **3:** 586, 1932.
28. Bernton, H. S., and Thom, C.: The Importance of Molds as Allergic Excitants in Some Cases of Vasomotor Rhinitis, J. ALLERGY **4:** 114, 1933.
29. Ellis, D.: The Incidence of Asthma in Port Sudan, With Special Reference to the Influence of Moulds, Guy's Hosp. Rep. **83:** 102, 1933.
30. Prince, H. E., Selle, W. A., and Morrow, M. B.: Molds in the Etiology of Asthma and Hay Fever, Texas State J. Med. **30:** 340, 1934.

31. Buchanan, E. D., and Buchanan, R. E.: Bacteriology, New York, 1930, Macmillan Co.
32. Thom, C., and Church, M. B.: The Aspergilli, Baltimore, 1926, Williams & Wilkins Co.
Thom, C.: The Penicillia, Baltimore, 1930, Williams & Wilkins Co.
33. Guilliermond, A., and Tanner, F. W.: The Yeasts, New York, 1920, John Wiley & Sons.
34. Sulzberger, M. B.: Experiments in Passive Transference of Urticarial Hypersensitiveness to Fungous Extracts, J. Immunol. **23**: 73, 1932.
35. Prausnitz, C., and Küstner, H.: Studien über die Ueberempfindlichkeit, Centralbl. f. Bakt. **86**: 160, 1921.
36. Cooke, R. A.: Studies in Specific Hypersensitiveness. IV. New Etiologic Factors in Bronchial Asthma, J. Immunol. **7**: 147, 1922.
37. Rowe, A. H.: House Dust in the Etiology of Bronchial Asthma and of Hay-Fever, Arch. Int. Med. **39**: 498, 1927.
38. Cohen, M. B.: Asthma Due to Household Articles, J. Lab. & Clin. Med. **14**: 837, 1929.
39. Storm van Leeuwen, W.: The Pathogenesis and Therapy of Bronchial Asthma, München. med. Wchnschr. **73**: 559, 1926.
40. Cohen, M. B., Nelson, T., and Reinarz, B. H.: Observations on the Nature of the House Dust Allergen, J. ALLERGY **6**: 517, 1935.

BLOOD SUGAR STUDIES IN HAY FEVER AND ASTHMA*

E. L. MacQuiddy, M.D., A. R. McIntyre, M.D., and Don Koser, A.B.
Omaha, Nebraska

IN 1925 James Adam[1] published a report of blood sugar determinations in 640 persons suffering from asthma and hay fever. He concluded that "the sugar content of asthmatic blood is frequently high, but without exact dieting, etc., definite conclusions cannot be drawn." Ramirez, St. George and Moses[2] examined the blood sugar of 40 patients, 28 of whom were suffering from asthma and hay fever. Determinations were made before and after treatment, and an examination of their findings reveals no uniform differences in the blood sugar level at these two periods. Malone[3] in 1929 examined the blood sugar level of 15 patients with allergic asthma associated with food allergy, and his figures yield an average fasting level of 75.4 mg. per cent, which he considers "low." Black[4] in 1933 reported 100 patients, all with a definite allergic history, and found an average fasting level of 78.9 mg. per cent. He maintained that "These findings would seem to justify the conclusion that more than half the asthma and hay fever patients have fasting blood sugar values below the normal limit and have definitely increased sugar tolerance."

In an effort to determine whether or not there was an alteration in sugar tolerance curves and in the fasting blood sugar levels of individuals suffering from asthma and hay fever, glucose tolerance tests were made on a number of patients and upon a group of 21 normal, nonallergic individuals at the allergy clinic, College of Medicine, University of Nebraska. No patients were included in this group who had taken adrenalin or ephedrine in the preceding twenty-four hours. About 20 blood sugars obtained were not listed in this series because of medication. One hundred gm. of dextrose was used routinely in glucose tolerance tests. This was always administered in the morning on an empty stomach and after at least eight hours of fasting. The patients were kept at rest for periods of at least ten minutes before the control blood samples were obtained. Emotional and other disturbances were eliminated as far as possible. For this reason routine urine samples were not obtained. In addition, a study was made of the effects upon the blood sugar level of epinephrine and dextrose when given separately and together.

The Hagedorn-Jensen micromethod as described by Peters and Van Slyke was selected because of the ease of obtaining blood samples and

*From the Allergy Department and Physiology Laboratory of the University of Nebraska College of Medicine.

because of the high degree of accuracy possible. It must be remembered in comparing the results here obtained with previous work that capillary blood obtained from the finger tip or ear is essentially the same as arterial blood in its glucose content. The peak figures presented in the following tables are approximately 20 per cent higher than the "peaks" would be in analysis of venous blood. This has been pointed out by Peters, Van Slyke and others. A total of 62 individuals was examined in these series. The normal (nonallergic) group was made up largely of medical students and assistants. The patients were divided into two groups on the basis of whether or not they were free from symptoms at the time blood samples were obtained. In establishing a normal fasting level in the first group a number of determinations were made on different days. The average fasting level of 101 mg. per cent is based on 38 different determinations. It is interesting to note that a variation of as much as 21 mg. per cent was found in five consecutive morning determinations in one subject of the normal (nonallergic) group.

TABLE I

NORMAL (NONALLERGIC) GROUP

NAME	FASTING LEVEL			PEAK	TIME IN MINUTES TO REACH PEAK
	LOW	HIGH	AVERAGE		
E. L. M.			92	208	30
D. C.	83	102	93	154	30
B. C.	93	106	101	150	30
J. M.	106	111	109	209	30
D. R.	95	106	100	139	30
D. K.	88	92	90		
C. R. S.	80	101	90	180	30
D. H.	107	114	111	198	30
J. W.	83	84	84	180	30
C. W. H.	104	120	112	193	30
J. M.	101	103	102	146	30
L. T.	120	127	123	156	60
P. T.	87	88	88	165	30
R. F.	110	118	114	202	30
H. F.	90	98	94	158	30
J. H.	92	102	97	172	30
S. H.	92	92	92	175	30
C. H. W.	104	108	106	195	30
J. F.	100	106	103	159	60
F. O.	98	100	99	178	30
G. C.	120	124	122	208	30
Average			101	171	33

DISCUSSION

Examination of the results obtained by previous workers in this field reveals a lack of unanimity of opinion. This is not surprising in view of the fact that no uniformity exists as far as methods and technic are concerned. As will be seen from Table I there is considerable variation in the fasting level of the same individual when determinations are made on consecutive days in the same laboratory using the same method and the same kind of blood. And furthermore, there is considerable dif-

ference in the values obtained when the same blood is tested by different methods. As with the normal control group there was a variation in the fasting blood sugar level of the allergic patients. This was true whether the test was run between attacks (Table II) or during attacks (Table III). This variation is also found in the peak values obtained.

TABLE II

ALLERGIC (SYMPTOM FREE GROUP)

NAME	AILMENT	FASTING LEVEL	PEAK LEVEL	MINUTES TO REACH PEAK LEVEL
G. B.	Asthma	108	177	60
R. G.	Hay fever	117	214	30
B. M.	Hay fever	110	161	30
R. D.	Asthma	102	204	60
H. W. C.	Hay fever	97	173	60
F. C.	Asthma	98	188	60
M. S.	Hay fever	104	191	30
M. W.	Asthma	113	173	30
W. B.	Asthma	81	210	60
M. H.	Hay fever	83	173	30
A. S.	Hay fever	95	161	60
A. A.	Asthma	99	181	30
C. S.	Asthma	100	175	90
F. H.	Asthma	64	192	60
M. Y.	Hay fever	83	144	30
M. H.	Asthma	105	162	30
J. S.	Hay fever	110	159	60
C. M.	Asthma	105	164	90
M. L.	Hay fever	82	139	30
M. M.	Hay fever	136	200	60
E. F.	Hay fever	110	161	60
	Average	100	176.3	50

TABLE III

ALLERGIC (GROUP MANIFESTING SYMPTOMS)

NAME	FASTING LEVEL	PEAK	MINUTES TO REACH PEAK
M. H.	90	125	60
M. U.	108	157	30
M. D.*	106	148	30
M. M.	108	171	60
M. S.	101	146	30
R. A.	87	158	30
P. M.	78	143	30
E. T.	88	157	60
M. J.	68	179	30
H. N.	102	183	60
M. S.	86	---	--
M. B.	91	179	60
M. E.	103	193	60
M. S.	101	159	60
J. B.	101	148	30
M. W.	105	153	30
F. C.	102	146	30
H. H.	90	183	60
M. S.	101	171	30
J. K.	97	181	30
Average	95.5	161.5	42.5

*Asthma.

CONCLUSION

In the data here presented we were unable to find any significant difference between the normal and the allergic individual in regard to their fasting blood sugar levels, or in their response to the ingestion of 100 gm. of dextrose.

NOTE.—This work was made possible by a grant from the Frederick Stearns Company.

REFERENCES

1. Adam, James: Am. Med. **31**: (N.S.) 328, 1925.
2. Ramirez, M. A., St. George, A. V., and Moses, R. L.: J. Lab. & Clin. Med. **10**: 199, 1924.
3. Malone, J. T.: U. S. Vet. Bureau, M. Bull. **5**: 285, 1929.
4. Black, J. H.: Texas State J. Med. **29**: 257, 1933.

HETEROPHILE ANTIGEN CONTENT OF POLLEN*

A Negative Report

Paul D. Garvin, M.D., and Stanley K. Kurland
Denver, Colorado

FOLLOWING the discovery by Forssman[1] in 1911 of heterophile antigen in the tissues of the guinea pig, it has been reported in other animal tissues and in certain bacteria. The subject, however, remained one of academic interest until the discovery by Davidsohn[2] of heterophile antibody in high titer in the sera of individuals who had received horse serum, with or without subsequent serum sickness reaction.

Further interest in heterophile antibody was stimulated by the work of Paul and Bunnell,[3] who reported a marked increase of this antibody in the sera of individuals suffering from infectious mononucleosis, and suggested the phenomenon as a valuable diagnostic test for this condition. Recently, several articles have appeared in the literature[4, 5] suggesting that the presence of heterophile antigen in certain bacteria, notably the pneumococcus, plays an important part in the antigenic efficiency of these bacteria; also that the production of the heterophile antibody in the immunized individual is of importance in determining the degree of immunization. These conclusions, however, as applied to the prophylaxis and treatment of pneumonia have been questioned by Finland and his associates.[6]

A fairly comprehensive search of the literature has revealed no report on the heterophile antigen content of pollen, and since pollen extracts have been used extensively in the treatment of hay fever, the possible presence or absence of heterophile antigen in these extracts led to the investigation outlined in the following experiments.

Blood taken from six otherwise healthy hay fever patients before treatment with pollen extract was tested for heterophile antibody content by titrating the serum for sheep cell agglutinin, following the technic of Paul and Bunnell.[3] The sera of all of the individuals showed the normal amount of sheep cell agglutinin before treatment, agglutinating the cells in a 1:4 dilution. Skin tests for sensitivity showed each of the patients sensitive to some of the following pollens occurring in the Denver area: Russian thistle, pasture sage, red root pigweed, short, giant and Western ragweed, and timothy grass. All six patients received between 20 and 25 doses of pollen extract, totaling approximately 40,000 Noon units. The average duration of treatment was approximately ten weeks.

*From the Department of Clinical Pathology, University of Colorado, School of Medicine.

On completion of treatment, blood was again taken and the heterophile antibody content of the sera determined, using the same technic as given above. In no instance was there any evidence of an increase of the heterophile antibody content in the sera of the treated individuals.

An attempt was then made to develop heterophile antibody in rabbits by injecting concentrated pollen extract intravenously. One rabbit was given 1.0 c.c. of 1:100 concentration of Russian thistle extract at five-day intervals for four doses. Another rabbit received the same dosage of giant ragweed at the same intervals. Five days after the last injection the animals were bled and the sera tested for sheep cell agglutinin, along with the control sera taken from the rabbits before the first injection. The sera taken before injection showed a titer of 1:4. The sera taken after injection showed the same titer. There was no increase in heterophile antibody content following the injection of large amounts of concentrated pollen extract.

CONCLUSIONS

From this study it would appear that pollen extracts used in the treatment of hay fever do not contain heterophile antigen. Consequently, the formation of heterophile antibody does not enter into the mechanism of desensitization of hay fever patients with pollen extracts.

REFERENCES

1. Forssman, J.: Die Herstellung hochwertiger specifischer Schafhämolysine ohne Verwendung von Schafblut, Biochem. Ztschr. **37**: 78, 1911.
2. Davidsohn, I.: Heterophilic Antibodies in Serum Sickness, J. Immunol. **16**: 259, 1929.
3. Paul, J. R., and Bunnell, W. W.: The Presence of Heterophilic Antibodies in Infectious Mononucleosis, Am. J. M. Sc. **183**: 90, 1932.
4. Rockwell, G. E., and Van Kirk, H. C.: The Relation of Heterophilic Immunity to the Incidence of Colds, J. Immunol. **28**: 475, 1935.
5. Shorb, M. S., and Bailey, G. H.: Heterophile Antigen in Various Bacterial Species, Am. J. Hygiene **19**: 148, 1934.
6. Finland, M., Ruegsegger, J. M., and Felton, L. D.: Should Heterophile Antibody Be Used in the Treatment of Pneumococci Pneumonia? J. A. M. A. **105**: 1180, 1935.

CRITIQUE OF THE PERENNIAL TREATMENT OF POLLEN ALLERGY*

M. Murray Peshkin, M.D.
New York, N. Y.

THE introduction of a modified or new form of treatment that gives promise of enhanced therapeutic usefulness is always an event of interest to the practitioner. Careful detailed clinical observations extended over a sufficient period of time on a large number of patients are indispensable requirements before lending encouragement to the widespread application of any therapeutic measure. The usefulness of a large majority of therapeutic innovations has sooner or later been circumscribed by certain limitations and disadvantages. With these thoughts in mind an attempt has been made in this study to evaluate the perennial or continuous treatment of pollen allergy.

In 1920 Walker[1] stated: "If pollen cases were treated as long and as consistently as the animal hair protein cases, many patients would possibly be free from symptoms entirely for years if not throughout life." The clinical application, however, of this principle of continuous treatment to patients suffering with pollen allergy was not commonly employed until quite recently. The perennial treatment of pollen allergy aims to maintain the patient's tolerance gained by the injection of pollen extracts prior to a pollen season. At the end of the pollen season maximal or near maximal doses of pollen are continued indefinitely at intervals of two to four weeks. In view of the widespread interest created in this subject and the almost uniform agreement in the statements made by the majority of workers with special reference to the superiority of the perennial over the preseasonal method of treatment, a detailed analysis of these statements appearing in the literature is essential.

In 1926 Stewart[2] reported treating, since 1920, some of her patients with pollen allergy the year round, giving a small dose of pollen extract twice monthly. In another paper read before the Association for the Study of Allergy in 1926 and published in 1931, Stewart[3] reported good results with the perennial treatment in 12 children and 29 adults along with the statement that this treatment "would indicate that permanent relief may be secured. This is especially true with children."

In 1927 Brown,[4] independently of White, reported his method of perennial therapy commenced in 1920, and cited his experiences with

*Read before the Combined Meeting of the Society for the Study of Asthma and Allied Conditions and the Association for the Study of Allergy, Atlantic City, June 10, 1935.

14 patients under treatment from two to five years. He stated that "in no instance has a patient under annual treatment fared worse than with his previous preseasonal treatment." Moreover, the claim was advanced that the possibility of occurrence of constitutional (general) reactions upon changing from an old (Coca) extract to a new and more potent one has been satisfactorily overcome by his method of mixing old and new extracts. In a second report in 1932 Brown[5] stated that constitutional reactions were found to appear less often than they did under preseasonal treatment, about one in every 200 injections. Thirteen of the 43 patients comprising the report were injected at intervals ranging from two to three weeks, averaging about 20 injections per patient. The remaining patients were on a monthly or four-week schedule. In all cases the cutaneous reaction to pollen remained positive. Twenty-one general (constitutional) reactions occurred in 10 patients, or 23 per cent of the series. The interval between injections bore no relationship to the frequency of general reactions which made their appearance anywhere between the first to the seventh year of perennial treatment despite added experience and the extra precautions taken to prevent such reactions. In a recent communication based on fourteen years' experience with the perennial treatment, Brown[6] stated that this method offers a good means of obtaining better results than with the preseasonal treatment and better hopes for permanent results.

In 1927 Vander Veer, Cooke and Spain[7] stated that while the then present method of treatment was very satisfactory, as far as relief of symptoms was concerned, they could not feel that they had reached their goal until they could promise a reasonable hope of permanent cure. The difficulties which these authors experienced with perennial treatment in 1920 were largely overcome with the introduction of Coca's solution for the extraction of pollen. Fifty patients were treated; 86 per cent reported satisfactory results on preseasonal treatment, while 95 per cent were satisfactory after a year of monthly injections. General reactions were five times more frequent, occurring in 0.66 per cent of the injections with perennial treatment as compared with 0.13 per cent the year before in the same cases on preseasonal treatment.

Kahn[8] has for years been obliged to employ a form of perennial treatment and has given maximal doses at intervals of from one to three weeks indefinitely. A variation is the injection of one-tenth to one-fourth of the maximum dose weekly and to increase the amount to maximal doses gradually some weeks before the usual time of onset. This method is often the only satisfactory form of treatment in the southwest and on the Pacific coast,[9] since pollen is in the air the greater part of the year. The question of whether or not this type of perennial treatment in patients more or less continually inhaling pollen is com-

parable with the usual form of perennial treatment in patients inhaling pollen only a few months of the year, may be answered by future studies.

Vaughan[10] stated that perennial therapy far excels either the preseasonal or the coseasonal methods. After the termination of the pollen season the dose of pollen is dropped from a customary 0.5 c.c. of a 1:50 extract to 0.1 c.c., and injections are given at intervals of two weeks until two or three months before the next season when each dose is increased 0.1 c.c. so that at the beginning of pollination the maximum desired dose has been reached. Twenty-one patients were treated perennially with either good or excellent results, but the total number of injections was a little greater than in preseasonal treatment. With the perennial method there occurred a decreased tendency to unfavorable reactions, none of which were severe. The incidence of general reactions was not reported.

Figley[11] reported a series of 65 patients on perennial treatment over a period of two to four years. In patients classed as sensitive and very sensitive the dose was decreased from the maximum after the pollen season, and injections were given monthly until about six weeks before the next season, when this maintenance dose was stepped up at weekly intervals until the maximal dose was again attained just before the onset of the pollen season (about 21 injections were given with this plan of perennial therapy). For less sensitive patients, monthly injections of the maximal dose were given. One general reaction occurred in about every 200 injections, none being severe or alarming. In a subsequent paper Figley[12] reported that in Ohio it required a maximum dose of 0.75 c.c. to 1 c.c. of a 1:50 dilution of pollen to protect satisfactorily a case of average sensitiveness. In that report 125 patients were treated by the perennial method over a period of two to five years. His previous ratio of one general reaction to 200 injections has been reduced by the practice of combining 0.1 c.c. of a mixture of ephedrine and epinephrine with each dose of pollen extract. The new ratio of general reactions to injections was not stated. The conclusions in favor of the perennial treatment are that the results are invariably better than those with the preseasonal method and that the clinical results improve directly in proportion to the length of continuous treatment.

Unger[13] reported 38 patients in whom the results ranged from improved to excellent in 94.8 per cent as compared with another group of 50 patients on preseasonal treatment in whom the results were 76 per cent. Employing perennial treatment as practiced by Vaughan,[10] Unger stated that not only were the results better with the perennial treatment, but the difference in constituitonal reactions was very striking. There were 34 general reactions in 18 patients or an incidence of 36 per cent of the patients during one year of preseasonal treatment as compared with three reactions or an incidence of 8 per cent in the perennial group.

Unger saw "no reason why we should not urge general practitioners to give perennial treatment."

Colmes[14] reported good results in 91 per cent of a series of 34 patients on perennial treatment as compared with 88 per cent in the same group on preseasonal treatment the preceding year. Most of the patients on perennial treatment received injections at three-week intervals, while a few patients could not maintain tolerance any longer than two weeks. All patients were given weekly treatments throughout the pollinating season (about 21 injections were administered to most patients). In about 12 per cent of the cases the results obtained by the perennial method were inferior to those produced by the preseasonal method of treatment. The number of treatments per patient was greater with the perennial method. General reactions occurred with slightly greater frequency in the perennially treated group. Colmes concluded that the perennial method of pollen therapy is not infallible.

Thommen[15] in a series of 70 patients on perennial treatment found that the total number of injections with this method was not decreased over the preseasonal treatment and that a decided increase in the number of clinical cures with the perennial method did not occur. General reactions were encountered more frequently with the perennial treatment than with the standard method.

Many contentions have been advanced in favor of or against the perennial treatment. The majority of these certainly cannot be dignified as scientific conclusions, some of which are as follows: The likelihood of interruption of treatment is minimized. The load of work which preseasonal pollen treatment places on the physician is distributed throughout the year. One worker finds that the greatest objection to perennial treatment is a psychologic one because indefinite uninterrupted attendance to a doctor's office, no matter how infrequent the visits, is liable to discourage the patient after carrying on such a performance one or two years. The patient becomes tired of the doctor and the doctor becomes tired of the patient. An objection advanced against the preseasonal method is that "the task of building a patient's resistance against pollen is a laborious one, for both the patient and the physician. It is, therefore, unfortunate if the tolerance so dearly gained be allowed to lapse." To other workers the perennial method is merely a convenient one.

The advantages of any form of treatment cannot conceivably be based on any one of the foregoing statements. As a matter of fact, our main concern with perennial treatment is whether or not it is productive of greater relief than the preseasonal method; whether or not perennial treatment can be applied without restriction to all patients with pollen allergy; whether or not this form of treatment can be applied to the patient without subjecting him to increased danger of undesirable general reactions; and finally, whether or not there exists in some

patients on perennial treatment the possibility of eventual tissue injury resulting in organic changes.

In 1932 I[16] ventured the following statement: "Under the preseasonal plan of treatment the organism has at least a six months' respite from injections. During this rest period the body is afforded an opportunity to undo any damage that may have occurred. Under the perennial plan of treatment a patient is subjected to the injection of a foreign substance year in and year out. We are all familiar with the organic changes occurring in animals as a result of injections of a foreign protein over prolonged periods of time. How much harm the perennial treatment will do cannot possibly be determined in two years. Perhaps five years from now adverse reports may creep into the literature. . . . The perennial plan of treatment may prove to be less troublesome, more economical, and more efficacious than the preseasonal plan. In spite of these attributes, along with the fact that the new plan of treatment holds a promise of a cure from pollen asthma and hay fever, we should nevertheless caution that this form of treatment is merely in the stage of clinical experimentation and is to be applied by trained allergists only. If I have given the impression that I do not employ the perennial treatment, I wish to state that this is not correct. I merely wish to point out the possible dangers involved and also to curb its widespread use until such time when the treatment and its effects are better understood."

These thoughts stimulated the present study along the following lines.

MATERIAL AND METHODS

This study is based on 100 patients with pollen allergy ranging in age from four to sixty years (60 adults and 40 children). Sixty-two patients had hay fever with or without pollen asthma, and the remaining 38 had perennial asthma with pollen allergy. The pollen sensitivities in the 100 patients were as follows: trees, 4 cases; grasses, 50 cases; and ragweed, 84 cases, totaling 138 cases, counting each season of each patient as a separate case. These 138 cases (with the exception of seven cases which experienced poor results in their last year of preseasonal treatment) were especially ideal subjects for perennial treatment because they obtained definite relief from symptoms of pollen allergy with the usual method of therapy. It was therefore felt that the results from perennial therapy in these cases should at least be equal to that obtained with preseasonal treatment.

The majority of the patients, with the exception of a small number of adults with hay fever, were also routinely tested to food and inhalant substances. Dietetic, environmental, and other necessary corrections were equally maintained throughout the preseasonal and perennial periods of treatment. As a matter of fact, by the time most of the patients came to perennial treatment they were in much better condi-

tion from the standpoint of allergy than when they first came for preseasonal treatment. Many of the perennial asthmatic individuals were also reduced to seasonal pollen asthmatic patients, but the initial diagnosis was maintained to avoid confusion.

The average number of injections required to reach the optimum or maximum protection dose, including the doses administered throughout the pollinating season with the preseasonal method of treatment, was 37 per patient as compared with 26 injections with the perennial method. It did not seem to matter whether the patients were highly sensitive or even negative to cutaneous tests (scratch and intradermal technics), the number of injections per course of treatment remained approximately the same. The patients were not classified according to their degree of skin sensitivity because neither has such a classification proved to be a reasonably reliable clinical working guide to protective dosage, nor is there any scientific evidence at hand which conclusively proves that the degree of cutaneous sensitivity parallels constitutional sensitivity. Protection doses are arrived at by individualization of treatment plus the experience of the worker behind the hypodermic syringe. A perusal of the protocol showing the maximum doses of pollen extracts injected and the test reactions in the 100 patients comprising this series will readily convince one that individualization of treatment is the only guide to satisfactory results.

The principle underlying the preseasonal treatment of pollen allergy is that of building up a tolerance against the pollen to which a patient is specifically sensitive. The local reactions to the subcutaneous injection of pollen are the most reliable guides to sensitivity as well as treatment. For practical purposes the treatment is begun with 0.05 c.c. of a 1:50,000 (1 pollen unit or 0.1 c.c. of 0.0001 mg. N per c.c.) dilution. After the initial dose of pollen is given, and depending entirely upon the patient's response to the treatment, the succeeding doses are gradually or rapidly increased. The ideal method of treatment is to administer pollen up to the point of optimum tolerance, which in most sections of the country, for the average patient, is approximately 0.5 c.c. of a 1:50 dilution. Many of these patients can take still higher dosage without experiencing any ill effects until the threshold of maximum tolerance is passed. The range from optimum to maximum tolerance frequently varies from 0.5 c.c. to 1.5 c.c. of a 1:50 dilution. This wide range of dosage, within the limits of which one can treat with safety, accounts for the equally wide divergence of opinion among allergy workers as to what actually constitutes the optimum protection dose. The optimum protection dose in the acutely hypersensitive patient may range from 0.1 c.c. of 1:5,000 to 0.5 c.c. of 1:500 dilution or even higher. The patient with pollen allergy refractory to the cutaneous tests (scratch and intradermal technics) usually requires and tolerates from 1 c.c. to 2 c.c. of 1:50 dilution of pollen extract. The guide to increasing dosage in the majority of patients is the absence

or almost complete absence of a local reaction at the site of the injection. It should be borne in mind, however, that general reactions may occur in spite of the absence of any local reaction and even in patients refractory to the cutaneous tests.

With the tolerance dosage known because of the preseasonal treatments administered to all of the patients comprising this series, one feels better prepared to cope with this phase of the problem when placing such a group on perennial treatment. With the latter method the biweekly interval between injections was chosen merely as a precautionary measure. At times and for various reasons, patients frequently came at three-week intervals, less frequently at monthly and only occasionally at even longer intervals. The maximum dose given during the preceding pollen season was dropped approximately 50 per cent, and this latter dose was maintained during the perennial course of treatment until several months prior to the onset of the next pollen season, when the dose was gradually stepped up, where possible, to its previous maximum level. If symptoms of pollen allergy became the least bit troublesome during the pollinating season, the interval between injections was shortened to one week, and frequently it was also found necessary to reduce the dose.

The pollen extracts were prepared after the method of Coca.[17] The maximum concentration was a 1:50 dilution, which since 1924 has been freshly prepared at least every two months. During the rush months of practice the extract was prepared at intervals of one to two weeks. The well-known dangers of changing from an old to a new extract were thus entirely eliminated. The ragweed extract consisted of equal parts of short and giant ragweed. The grass extract contained equal parts of timothy, red top, orchard and June grasses.

All patients were first tested by the scratch technic with dry powdered natural pollens or a 1:50 extract. When the scratch tests were negative, intradermal tests with the 1:50 extracts were next performed and finally the dry pollen eye test.[18] The pollens of short and giant ragweed, timothy, red top, orchard and June grasses, plantain, and the trees were routinely employed for testing. The results of these tests according to season—ragweed, grasses and the trees—are recorded in the protocol. The patients were tested many more times than is shown in the protocol, but only the initial, final and important interval reactions were recorded. Subsequent test reactions showing no important change from the initial test were not recorded. When the intradermal test was negative to the four grasses mentioned, the dry pollen eye test not infrequently would be positive to two or three and occasionally to only one grass. To avoid confusion and since this finding is not pertinent to this paper, the eye test reactions recorded under grasses were marked as positive, giving the impression that all the grasses were positive even though only one of the grasses was positive. This phenomenon was previously reported[19] and is of some significance.

PROTOCOL

CASE NUMBER	AGE FIRST SEEN	PRESEASONAL TREATMENT*					PERENNIAL TREATMENT					POLLEN TEST REACTIONS†				
		GRASSES			RAGWEED		GRASSES			RAGWEED						
		POLLEN YEAR	MAXIMUM DOSE INJECTED‡	RELIEF IN PER CENT	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT§	POLLEN YEAR	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT	DATE	POLLEN SEASON	SCR.: DRY POLLEN, 1:50 EXT.	INTR.: COCA, 1:50 EXT.	EYE: DRY POLLEN
								Hay Fever (Adults)								
1	33	1932	(A) 0.6 c.c.	90			1933	(A) 0.6 c.c. (B)				1/18/32	oak	–	–	++
		1933	(A) 0.34 c.c.	90									ash	–	–	++
		1934	(A) 0.44 c.c.	75								2/15/35	oak	–	–	++
													ash	–	–	++
2	45	1928	2.0 c.c.	75			1933	(C) 0.45 c.c.	90			6/13/27	grasses	++		
		1929	1.6 c.c.	75			1934	(C) 0.45 c.c.	90				plantain	++++		
		1930	1.4 c.c.	75								3/ 3/31	grasses	–	–	+++
		1931	(C) 0.8 c.c.	90									plantain	++++		
		1932	(C) 0.45 c.c.	90								9/ 5/34	grasses	–	–	+++
													plantain	++++		
3	35	1927	1.45 c.c.	75	0.75 c.c.	50	1933	(D) 0.45 c.c.	100	0.6 c.c.	90	11/19/26	plantain	++		
		1928	2.0 c.c.	75	0.8 c.c.	90	1934	(D) 0.45 c.c.	90	0.6 c.c.	100		grasses	–	–	++
													ragweed	+		
		1929	1.2 c.c.	75	1.0 c.c.	50						1/22/31	plantain	+		
													grasses	–	–	+
													ragweed	–	–	+
		1930	0.6 c.c.	75	0.75 c.c.	90						10/16/34	plantain	–	++	+++
		1931	(D) 0.55 c.c.	90	0.7 c.c.	100							grasses	–	–	–
		1932	(D) 0.45 c.c.	90	0.7 c.c.	100							ragweed	–	–	–
4	25	1932	0.005 c.c.	0			1933	0.006 c.c.	50			2/ 6/32	grasses	++++		
							1934	0.006 c.c.	75			4/13/35	grasses	+++		

5	35	1929	0.8	c.c.	90	0.5	c.c.	90	1933	0.4	c.c.	90	0.5	c.c.	90	2/15/29	grasses	++++		
																	ragweed	++++		
		1930	0.7	c.c.	90	0.5	c.c.	90	1934	0.4	c.c.	75	0.5	c.c.	90	11/20/33	grasses	−	+++	
																	ragweed	−	++	
		1931	0.55	c.c.	75	0.5	c.c.	90								12/20/34	grasses	−	+++	
		1932	0.4	c.c.	100	0.5	c.c.	90									ragweed	−	+++	
6	27	1931	0.2	c.c.	90	0.18	c.c.	90	1933	0.2	c.c.	100	0.2	c.c.	100	3/14/31	grasses	++++		
																	ragweed	++++		
		1932	0.2	c.c.	100	0.2	c.c.	100	1934	0.2	c.c.	90	0.2	c.c.	100	11/14/34	grasses	+		
																	ragweed	++		
7	38	1929				1.0	c.c.	90	1932				0.6	c.c.	100	9/ 4/28	ragweed	++++		
		1930				0.8	c.c.	100	1933				0.6	c.c.	100	7/29/31	ragweed	+		
		1931				0.75	c.c.	100								10/ 2/33	ragweed	+		
8	26	1930	0.6	c.c.	90	0.32	c.c.	0	1933	0.4	c.c.	90	0.3	c.c.	50	11/ 9/29	grasses	+		
																	ragweed	++++		
		1931	0.6	c.c.	90	0.38	c.c.	0	1934	0.32	c.c.	90	0.34	c.c.	0	2/ 6/31	grasses	−	+	++
																	ragweed	++++		
		1932	0.52	c.c.	100	0.34	c.c.	90								2/ 9/32	grasses	−	−	++
																	ragweed	+++		
																11/21/34	grasses	−	−	+
																	ragweed	++		
9	36	1930				0.2	c.c.	75	1932				0.08	c.c.	75	6/24/30	ragweed	++++		
		1931				0.2	c.c.	75	1933				0.05	c.c.	0	6/28/34	ragweed	++++		
									1934			(E)	0.05	c.c.	0	4/ 4/35	ragweed	++++		
10	37	1932				0.11	c.c.	75	1934				0.08	c.c.	50	3/31/32	ragweed	++		
		1933				0.08	c.c.	75								12/ 5/34	ragweed	+++		
11	26	1932	0.14	c.c.	50				1933	0.2	c.c.	100				10/12/31	grasses	++		
									1934	0.2	c.c.	90				10/31/34	grasses	±	++	
12	32	1928				0.04	c.c.	50	1932				0.12	c.c.	90	3/26/28	ragweed	++++		
		1929				0.10	c.c.	75	1933				0.10	c.c.	50	2/ 5/32	ragweed	+		
		1930				0.13	c.c.	90	1934				0.10	c.c.	90	3/ 2/35	ragweed	+		
		1931				0.13	c.c.	90												
13	27	1931				0.5	c.c.	75	1932				0.45	c.c.	90	4/21/31	ragweed	++++		
																9/29/32	ragweed	+++		

PROTOCOL—CONT'D

CASE NUMBER	AGE FIRST SEEN	PRESEASONAL TREATMENT*					PERENNIAL TREATMENT					POLLEN TEST REACTIONS†				
			GRASSES		RAGWEED			GRASSES		RAGWEED						
		POLLEN YEAR	MAXIMUM DOSE INJECTED‡	RELIEF IN PER CENT	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT§	POLLEN YEAR	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT	DATE	POLLEN SEASON	SCR.: DRY POLLEN, 1:50 EXT.	INTR.: COCA, 1:50 EXT.	EYE: DRY POLLEN
14	17	1929			1.0 c.c.	100	1932			0.7 c.c.	100	9/21/28	ragweed	++		
		1930			0.75 c.c.	100						7/29/31	ragweed	±		
		1931			0.6 c.c.	100						3/25/32	ragweed	−	+++	
15	26	1930	0.6 c.c.	50			1931	0.4 c.c.(F)				3/ 8/30	grasses	±	++	
		1931	0.8 c.c.	75								2/19/32	grasses	−	+	++
		1932	0.6 c.c.	50												
16	26	1931	0.1 c.c.	50			1934	0.06 c.c.	50			3/12/31	grasses	++++		
		1932	0.1 c.c.	50								10/23/34	grasses	+		
		1933	0.1 c.c.	50												
17	52	1930	1.0 c.c.	100	0.65 c.c.	90	1933	1.0 c.c.	100	0.6 c.c.	100	2/21/30	grasses	++++		
		1931	1.0 c.c.	100	0.65 c.c.	90	1934	1.0 c.c.	100	0.5 c.c.	100		ragweed	++++		
		1932	1.0 c.c.	100	0.65 c.c.	100						8/31/32	grasses	+		
													ragweed	+		
												6/29/34	grasses	−	+	+++
													ragweed	−		
												10/26/34	grasses	−	+	+++
													ragweed	±	++	
18	19	1930	0.06 c.c.	90			1933	0.035 c.c.	75			2/ 7/30	grasses	++		
		1931	0.08 c.c.	90								2/23/32	grasses	+		
		1932	0.04 c.c.	90								5/22/33	grasses	+		

19	22	1926	1.0	c.c.	75				1933	0.32	c.c.	100				6/ 3/25	grasses	++++		
		1927	1.0	c.c.	100				1934	0.24	c.c.	90				2/17/32	grasses	++		
		1928	1.0	c.c.	90											10/24/34	grasses	+		
		1929	0.8	c.c.	100															
		1930	1.0	c.c.	90															
		1931	0.7	c.c.	100															
		1932	0.65	c.c.	100															
20	22	1929				1.0	c.c.	100	1932				0.65	c.c.	100	4/12/29	ragweed	++++		
		1930				0.75	c.c.	100	1933				0.6	c.c.	100	9/21/32	ragweed	++++		
		1931				0.75	c.c.	100								9/ 9/33	ragweed	++++		
21	30	1929				0.8	c.c.	50	1932				0.6	c.c.	90	9/21/28	ragweed	++++		
		1930				0.65	c.c.	75	1933				0.6	c.c.	90	10/21/32	ragweed	±		
		1931				0.65	c.c.	90	1934				0.6	c.c.	90	7/ 7/31	ragweed	−	+++	
																12/24/34	ragweed	±	+++	
22	53	1931				0.12	c.c.	75	1932				0.08	c.c.	90	11/ 3/30	ragweed	++		
									1933				0.08	c.c.	90	10/ 4/32	ragweed	+++		
									1934			(G)	0.08	c.c.	0	3/18/35	ragweed	+		
23	36	1931	1.0	c.c.	100	0.55	c.c.	90	1933	1.0	c.c.	100	0.55	c.c.	100	3/15/30	grasses	−	+	+++
		1932	1.0	c.c.	100	0.5	c.c.	100	1934	1.0	c.c.	100	0.6	c.c.	100		ragweed	+++		
																9/23/32	grasses	−	+	+++
																	ragweed	++		
																12/27/34	grasses	−	−	−
																	ragweed	++		
									Hay Fever (Children)											
24	8	1931				0.6	c.c.	100	1932				0.6	c.c.	90	3/ 6/31	ragweed	±		
									1933				0.6	c.c.	90	10/17/33	ragweed	±		
									1934				0.6	c.c.	100	4/16/35	ragweed	−	++	+++
25	7	1933				0.3	c.c.	50	1934				0.3	c.c.	50	2/18/33	ragweed	+		
																11/13/34	ragweed	−	+	++

PROTOCOL—CONT'D

CASE NUMBER	AGE FIRST SEEN	PRESEASONAL TREATMENT*					PERENNIAL TREATMENT					POLLEN TEST REACTIONS†				
			GRASSES		RAGWEED			GRASSES		RAGWEED						
		POLLEN YEAR	MAXIMUM DOSE INJECTED‡	RELIEF IN PER CENT	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT§	POLLEN YEAR	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT	DATE	POLLEN SEASON	SCR.: DRY POLLEN, 1:50 EXT.	INTR.: COCA, 1:50 EXT.	EYE: DRY POLLEN
26	13	1932	0.5 c.c.	100	0.25 c.c.	90						10/14/31	grasses	++		
							1933 (H)	0.5 c.c.	100	0.22 c.c.	90		ragweed	++++		
		1934	0.6 c.c.	90	0.3 c.c.	100						9/19/32	grasses	+		
													ragweed	+		
												1/13/34	grasses	±		
													ragweed	±		
												10/27/34	grasses	±	+++	++++
													ragweed	±		
27	9	1932	0.32 c.c.	50			1933	0.24 c.c.	75			3/ 7/32	grasses	++++		
							1934	0.26 c.c.	90			2/13/34	grasses	++		
												1/12/35	grasses	+		
28	13	1931	0.24 c.c.	100	0.3 c.c.	90	1933	0.2 c.c.	90	0.24 c.c.	75	2/16/31	grasses	±	++	+++
		1932	0.32 c.c.	90	0.36 c.c.	90							ragweed	+		
												7/14/33	grasses	±	+	+++
													ragweed	+		
29	6	1928			0.5 c.c.	75	1933			0.07 c.c.	50	4/28/28	ragweed	++++		
		1929			0.42 c.c.	0						3/23/29	ragweed	±		
		1930			0.4 c.c.	50						8/ 5/31	ragweed	−	+++	
		1931			0.4 c.c.	0						3/28/32	ragweed	++		
		1932			0.1 c.c.	50						9/27/32	ragweed	−	++	+++
												2/13/33	ragweed	+		
30	6	1929			0.5 c.c.	50	1932			0.5 c.c.	100	5/18/29	ragweed	++++		
		1930			0.5 c.c.	90	1933			0.5 c.c.	90	9/14/31	ragweed	±		
		1931			0.5 c.c.	100	1934			0.5 c.c.	90	9/14/32	ragweed	−	+	+++
												11/ 4/33	ragweed	±		
												10/20/34	ragweed	±	+++	

31	8	1932				0.34	c.c.	75	1933				0.32	c.c.	50	12/ 7/31	ragweed	++		
																9/17/32	ragweed	±		
																2/ 5/33	ragweed	+		
																9/23/33	ragweed	+		
32	13	1931	0.4	c.c.	90	0.28	c.c.	75	1933	0.4	c.c.	90	0.19	c.c.	50	9/ 4/30	grasses	+++		
		1932	0.45	c.c.	100	0.20	c.c.	90	1934	0.34	c.c.	90	0.18	c.c.	0		ragweed	+++		
																1/ 9/32	grasses	+		
																	ragweed	++++		
																10/30/34	grasses	+		
																	ragweed	++		
33	8	1928	1.2	c.c.	90	1.0	c.c.	90	1933	1.0	c.c.	100	0.6	c.c.	100	11/ 7/27	grasses	+++		
		1929	1.4	c.c.	100	0.8	c.c.	90									ragweed	++++		
		1930			(I)			(I)								2/ 7/30	grasses	−	+	+++
		1931			(I)			(I)									ragweed	−	+	+++
		1932	1.0	c.c.	90	0.8	c.c.	100								2/18/32	grasses	−	−	+
																	ragweed	−	−	+++
																9/26/33	grasses	−	−	+
																	ragweed	−	−	+++
34	10	1927	1.6	c.c.	75				1933	0.6	c.c.	50				2/ 5/27	grasses	+		
		1928	1.5	c.c.	90				1934	0.6	c.c.	50				1/ 8/30	grasses	−	+	++++
		1929	1.6	c.c.	90											9/ 4/30	grasses	−	−	+++
		1930	1.0	c.c.	75											9/ 9/33	grasses	−	−	++
		1931	0.6	c.c.	75											7/ 3/34	grasses	−	−	+
		1932	0.6	c.c.	75															
Pollen Asthma With Hay Fever (Adults)																				
35	43	1929	(J) 0.16	c.c.	50	0.42	c.c.	50	1932	1.0	c.c.	90	0.8	c.c.	100	7/16/29	grasses	+	+++	
		1930	1.2	c.c.	90	0.9	c.c.	90	1933	1.0	c.c.	100	0.8	c.c.	100		ragweed	−	−	+
		1931	1.6	c.c.	90	0.9	c.c.	90	1934	1.0	c.c.	90	1.0	c.c.	100	2/ 2/31	grasses	−	++	+++
																	ragweed	−	−	−
																10/24/34	grasses	−	−	−
																	ragweed	−	−	−
36	35	1929				1.0	c.c.	75	1932				0.5	c.c.	100	3/26/29	ragweed	−	+	++
		1930				0.9	c.c.	75	1933				0.5	c.c.	100	3/13/30	ragweed	−	−	++
		1931				0.7	c.c.	100								10/11/33	ragweed	−	−	++

PROTOCOL—CONT'D

CASE NUMBER	AGE FIRST SEEN	PRESEASONAL TREATMENT*					PERENNIAL TREATMENT					POLLEN TEST REACTIONS†				
		GRASSES			RAGWEED		GRASSES			RAGWEED						
		POLLEN YEAR	MAXIMUM DOSE INJECTED‡	RELIEF IN PER CENT	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT§	POLLEN YEAR	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT	DATE	POLLEN SEASON	SCR.: DRY POLLEN, 1:50 EXT.	INTR.: COCA, 1:50 EXT.	EYE: DRY POLLEN
37	24	1925	0.5 c.c.	0	1.0 c.c.	50	1933	1.0 c.c.	90	0.5 c.c.	90	3/21/25	grasses	–	–	–
		1926	0.95 c.c.	50	0.9 c.c.	75							ragweed	–	–	+
		1927	1.7 c.c.	75	1.0 c.c.	50						2/ 4/30	grasses	–	–	–
		1928	2.0 c.c.	100	1.0 c.c.	100							ragweed	–	–	++
		1929	1.6 c.c.	100	0.8 c.c.	100						2/ 3/31	grasses	–	–	–
		1930	2.0 c.c.	100	0.6 c.c.	100							ragweed	–	–	–
		1931	1.0 c.c.	100	0.65 c.c.	90						10/ 9/33	grasses	–	–	–
		1932	1.0 c.c.	90	0.65 c.c.	90							ragweed	–	–	–
38	34	1920	0.01 c.c.	50			1933	0.035 c.c.	90			2/24/20	grasses	+++		
		1921	0.03 c.c.	0			1934	0.035 c.c.	75			2/17/32	grasses	++		
		1922	0.9 c.c.	50								3/26/35	grasses	++		
		1923	1.8 c.c.	0												
		1924	2.0 c.c.	75												
		1925	1.8 c.c.	50												
		1926	0.9 c.c.	75												
		1927	0.56 c.c.	0												
		1928	0.75 c.c.	75												
		1929	0.6 c.c.	0												
		1930		(K)												
		1931	0.6 c.c.	50												
		1932	0.03 c.c.	75												

39	24	1930				0.6	c.c.	90	1932			0.52	c.c.	90	3/11/30	ragweed	±	++	
		1931				0.6	c.c.	90	1933			0.52	c.c.	100	2/ 6/32	ragweed	+		
									1934			0.52	c.c.	100	10/11/33	ragweed	−	+	+++
															12/ 5/34	ragweed	−	−	++
40	29	1933				0.22	c.c.	50	1934			0.2	c.c.	100	6/ 1/33	ragweed	+		
															10/11/33	ragweed	±		
															10/17/34	ragweed	±		
41	28	1932				0.8	c.c.	50	1933			0.6	c.c.	0	10/16/31	ragweed	+++		
									1934			0.5	c.c.	50	8/21/32	ragweed	−	++	++++
															9/28/33	ragweed	−	++	++++
															11/16/34	ragweed	±	+++	++++
42	28	1931	1.6	c.c.	75	0.9	c.c.	75							4/ 7/31	grasses	−	−	−
									1932	1.35	c.c. 90	0.9	c.c.	0		ragweed	−	−	+
		1933	1.6	c.c.	75	1.0	c.c.	75							2/19/35	grasses	−	−	−
		1934	1.6	c.c.	90	1.0	c.c.	75								ragweed	−	−	++
43	51	1933				0.18	c.c.	50	1934			0.2	c.c.	50	4/24/33	ragweed	++++		
															9/ 4/34	ragweed	++		
44	30	1926				1.05	c.c.	75							10/29/25	ragweed	++++		
		1927				1.25	c.c.	75							9/27/32	ragweed	++		
		1928				1.0	c.c.	50							4/ 4/33	ragweed	+++		
		1929				0.8	c.c.	50							6/ 8/34	ragweed	+++		
		1930				0.6	c.c.	90											
		1931				0.65	c.c.	75											
									1932			0.65	c.c.	0					
		1933				0.50	c.c.	0											
		1934				0.6	c.c.	0											
45	47	1930	2.0	c.c.	50										1/24/30	grasses	−	−	−
		1931	2.0	c.c.	75										2/ 3/32	grasses	−	−	−
		1932	1.8	c.c.	75										1/11/34	grasses	−	−	−
									(L)	1933	1.8 c.c. 75				1/17/35	grasses	−	−	−
		1934	2.0	c.c.	75														
46	40	1932	0.88	c.c.	90	0.2	c.c.	90	1933	0.75	c.c. 75	0.2	c.c.	75	1/16/32	grasses	+++		
						(M)						(M)				hickory	+++		
									1934	0.60	c.c. 50	0.2	c.c.	50	11/ 3/34	grasses	−	+++	++++
												(M)				hickory	+		

PROTOCOL—CONT'D

CASE NUMBER	AGE FIRST SEEN	PRESEASONAL TREATMENT*					PERENNIAL TREATMENT					POLLEN TEST REACTIONS†				
			GRASSES		RAGWEED			GRASSES		RAGWEED						
		POLLEN YEAR	MAXIMUM DOSE INJECTED‡	RELIEF IN PER CENT	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT§	POLLEN YEAR	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT	DATE	POLLEN SEASON	SCR.: DRY POLLEN, 1:50 EXT.	INTR.: COCA, 1:50 EXT.	EYE: DRY POLLEN
47	35	1928			0.4 c.c.	90	1932			0.25 c.c.	90	12/20/27	ragweed	++++		
		1929			0.3 c.c.	90	1933			0.25 c.c.	75	7/17/31	ragweed	±		
		1930			0.35 c.c.	100						3/26/32	ragweed	+		
		1931			0.35 c.c.	100						10/11/32	ragweed	++		
												9/15/33	ragweed	+		
48	30	1932			1.0 c.c.	75	1933			1.0 c.c.	50	10/ 2/31	ragweed	−	−	++
							1934			1.0 c.c.	100	4/16/35	ragweed	−	+	++
49	22	1928	1.0 c.c.	75			1933	0.75 c.c.	100			6/16/27	grasses	++++		
		1929	1.0 c.c.	90								2/ 1/32	grasses	+		
		1930	1.0 c.c.	100								7/14/33	grasses	−	+	+++
		1931	1.0 c.c.	100												
		1932	1.0 c.c.	100												
50	32	1929			0.44 c.c.	75						3/13/29	ragweed	++++		
		1930			0.4 c.c.	90						4/28/31	ragweed	++++		
		1931			0.34 c.c.	90						7/28/31	ragweed	++		
							1932			0.26 c.c.	0	9/22/32	ragweed	++		
		1933			0.24 c.c.	75						9/25/34	ragweed	+		
		1934			0.22 c.c.	90										
51	40	1927			0.20 c.c.	75	1932			0.15 c.c.	50	4/20/27	ragweed	++++		
		1928			0.24 c.c.	50	1933			0.10 c.c.	50	4/ 7/31	ragweed	++		
		1929			0.28 c.c.	50	1934			0.11 c.c.	50	10/ 3/32	ragweed	+++		
		1930			0.20 c.c.	75						10/23/34	ragweed	++		
		1931			0.18 c.c.	0										

52	39	1928				0.8	c.c.	90	1932				0.8	c.c.	0	4/ 9/28	ragweed	++++		
		1929				0.8	c.c.	50								3/17/31	ragweed	++++		
		1930				0.9	c.c.	75								7/27/31	ragweed	+		
		1931				0.9	c.c.	0								9/19/32	ragweed	±		
53	31	1923				1.4	c.c.	75	1932				0.6	c.c.	90	12/ 8/22	ragweed	++++		
		1924				1.15	c.c.	75	1933				0.5	c.c.	75	3/16/31	ragweed	++		
		1925				1.05	c.c.	50	1934				0.55	c.c.	50	3/11/32	ragweed	+		
		1926				1.2	c.c.	0								12/12/33	ragweed	++		
		1927				1.2	c.c.	75								10/11/34	ragweed	±		
		1928				1.0	c.c.	0												
		1929				1.0	c.c.	50												
		1930				0.6	c.c.	75												
		1931				0.5	c.c.	90												
									Pollen Asthma With Hay Fever (Children)											
54	14	1932				0.09	c.c.	90	1933				0.08	c.c.	90	2/ 2/32	ragweed	++++		
									1934				0.09	c.c.	90	10/27/34	ragweed	++++		
55	8	1930				0.9	c.c.	50	1932				0.7	c.c.	75	11/15/29	ragweed	−	−	++
		1931				0.8	c.c.	75								3/11/31	ragweed	−	−	+
																6/24/32	ragweed	−	−	+
56	11	1928	1.9	c.c.	100	1.2	c.c.	90	1932	1.0	c.c.	50	0.7	c.c.	90	2/ 4/28	grasses	++		
		1929	1.7	c.c.	100	1.0	c.c.	90	1933	1.0	c.c.	100	0.65	c.c.	90		ragweed	++		
		1930	1.3	c.c.	90	0.9	c.c.	90	1934	1.0	c.c.	75	0.75	c.c.	100	2/13/31	grasses	±		
		1931	1.2	c.c.	100	0.85	c.c.	90									ragweed	+		
																9/15/33	grasses	±	++	+++
																	ragweed	−	−	+++
																10/19/34	grasses	−	−	++
																	ragweed	+		
57	4	1928	1.2	c.c.	100	1.15	c.c.	100	1933	1.0	c.c.	75	0.7	c.c.	90	1/23/28	grasses	−	−	+
		1929				1.0	c.c.	90	1934	1.0	c.c.	90	0.8	c.c.	90		ragweed	−	+	+
		1930	1.35	c.c.	100	0.9	c.c.	75								3/ 1/30	grasses	−	−	−
		1931	0.25	c.c.	75	0.7	c.c.	75									ragweed	−	−	+
		1932	1.0	c.c.	90	0.9	c.c.	90								10/ 1/34	grasses	−	−	−
																	ragweed	−	++	+++

PROTOCOL—CONT'D

CASE NUMBER	AGE FIRST SEEN	PRESEASONAL TREATMENT*					PERENNIAL TREATMENT					POLLEN TEST REACTIONS†				
			GRASSES		RAGWEED			GRASSES		RAGWEED						
		POLLEN YEAR	MAXIMUM DOSE INJECTED‡	RELIEF IN PER CENT	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT§	POLLEN YEAR	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT	DATE	POLLEN SEASON	SCR.: DRY POLLEN, 1:50 EXT.	INTR.: COCA, 1:50 EXT.	EYE: DRY POLLEN
58	11	1931	1.2 c.c.	90	0.8 c.c.	75	1933	1.0 c.c.	90	0.95 c.c.	90	8/28/30	grasses	+		
		1932	1.0 c.c.	100	0.9 c.c.	90	1934	1.0 c.c.	100	1.0 c.c.	90		ragweed	−	−	+
												2/13/32	grasses	−	−	−
													ragweed	−	−	++
												3/17/34	grasses	−	−	−
													ragweed	−	−	+
59	8	1931			0.75 c.c.	75	1932			0.6 c.c.	50	11/19/30	ragweed	+		
							1933			0.6 c.c.	90	7/ 7/31	ragweed	++		
							1934			0.8 c.c.	50	9/24/32	ragweed	−	+	++
												10/27/34	ragweed	−	+	+++
60	4	1929			0.8 c.c.	75	1932			0.6 c.c.	75	3/27/29	ragweed	++		
		1930				(N)	1933			0.65 c.c.	90	3/12/30	ragweed	±		
		1931			0.9 c.c.	0	1934			0.7 c.c.	90	10/22/30	ragweed	±		
												2/20/32	ragweed	−	+	+++
												11/26/34	ragweed	−	+	+++
61	10	1929			0.95 c.c.	100	1932			1.0 c.c.	90	3/27/29	ragweed	−	+	++
		1930			0.75 c.c.	50	1933			0.9 c.c.	75	3/15/30	ragweed	−	−	++
		1931			0.8 c.c.	75	1934			1.0 c.c.	0	3/21/31	ragweed	−	−	+
												4/ 3/34	ragweed	−	−	−
												3/13/35	ragweed	−	+	++

62	7	1931	1.0	c.c.	100	0.45 (O)	c.c.	50	1932	1.0	c.c.	75	0.6 (O)	c.c.	90	7/19/30	oak	+		
									1933	1.0	c.c.	75	0.7 (O)	c.c.	100		grasses	++++		
									1934	1.0	c.c.	100	0.6 (O)	c.c.	100	2/ 5/32	oak	−	++	
																	grasses	±		
																9/26/33	oak	−	+	+++
																	grasses	−	+	+++
																9/15/34	oak	+		
																	grasses	−	−	−

PROTOCOL—CONT'D

CASE NUMBER	AGE FIRST SEEN	PRESEASONAL TREATMENT*						PERENNIAL TREATMENT						POLLEN TEST REACTIONS†				
			GRASSES			RAGWEED			GRASSES			RAGWEED						
		POLLEN YEAR	MAXIMUM DOSE INJECTED‡		RELIEF IN PER CENT	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT§	POLLEN YEAR	MAXIMUM DOSE INJECTED		RELIEF IN PER CENT	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT	DATE	POLLEN SEASON	SCR.: DRY POLLEN, 1:50 EXT.	INTR.: COCA, 1:50 EXT.	EYE: DRY POLLEN
67	34	1930				0.35 c.c.	75	1932	1.0 c.c.		90	0.7 c.c.	90	7/ 2/30	grasses	–	–	++
		1931	1.0 c.c.		100	0.8 c.c.	90	1933	1.0 c.c.		100	0.4 c.c.	90		ragweed	++		
								1934	1.0 c.c.		75	0.4 c.c.	75	9/16/33	grasses	–	–	–
															ragweed	++		
														10/20/34	grasses	–	–	–
															ragweed	–	+	++
68	60	1930				0.6 c.c.	50	1932				0.32 c.c.	75	9/21/29	ragweed	+		
		1931				0.35 c.c.	75	1933				0.3 c.c.	75	10/27/34	ragweed	±	++	++++
								1934				0.3 c.c.	75					
69	44	1932	0.8 c.c.		75	0.2 c.c.	75							11/13/34	grasses	–	++	+++
								1933	0.65 c.c.		0	0.08 c.c. (R)	75		ragweed	+++		
		1934	0.8 c.c.		0	0.28 c.c.	75							1/ 9/34	grasses	–	++	+++
															ragweed	+++		
														2/18/35	grasses	–	++	+++
															ragweed	±		
70	59	1930	0.8 c.c.		90			1932	1.4 c.c.		75			8/21/29	grasses	–	–	+++
		1931	1.0 c.c.		50			1933	2.0 c.c.		100			1/17/31	grasses	–	–	–
								1934	2.0 c.c.		100			2/16/32	grasses	–	–	–
														3/ 2/35	grasses	–	–	–
71	45	1931	1.6 c.c.		90	0.85 c.c.	100	1932	1.2 c.c.		90	0.8 c.c.	90	9/ 4/30	grasses	–	–	–
								1933	1.0 c.c.		90	0.9 c.c.	90		ragweed	–	–	++++ (S)
								1934	1.0 c.c.		90	1.0 c.c.	100	3/ 4/32	grasses	–	–	–
															ragweed	–	–	+++
														4/ 3/35	grasses	–	–	–
															ragweed	–	–	++

72	52	1929				1.05	c.c.	75							9/17/28	ragweed	++		
		1930				0.7	c.c.	0							1/16/31	ragweed	+		
		1931				0.8	c.c.	75							7/30/31	ragweed	±		
									1932			0.6	c.c.	0	9/28/32	ragweed	±		
		1933				0.26	c.c.	50							2/ 7/33	ragweed	+++		
		1934				0.48	c.c.	50							1/11/34	ragweed	−	+	+++
															5/ 1/34	ragweed	−	−	+++
															3/25/35	ragweed	++		
73	17	1929				0.6	c.c.	90	1932			0.6	c.c.	90	9/26/28	ragweed	−	−	++
		1930				0.6	c.c.	90							3/14/30	ragweed	−	−	+
		1931				0.6	c.c.	90							3/17/32	ragweed	−	−	−
74	26	1932	1.0	c.c.	90	0.85	c.c.	90	1933	0.8	c.c.	90	0.8	c.c.	90	8/ 3/31	grasses	+		
																	ragweed	±		
																10/ 5/33	grasses	±	+++	
																	ragweed	−	++	+++
75	32	1931				0.18	c.c.	50	1932			0.12	c.c.	75	11/19/30	ragweed	+		
									1933			0.12	c.c.	0	1/31/33	ragweed	±		
76	32	1930				1.0	c.c.	75	1932			0.8	c.c.	90	9/13/29	ragweed	−	−	+++
		1931				1.0	c.c.	90	1933			0.7	c.c.	75	3/14/31	ragweed	−	−	+
									1934			0.8	c.c.	90	1/18/32	ragweed	−	−	+++
															4/ 8/35	ragweed	−	−	−
77	18	1931				0.18	c.c.	50	1934			0.10	c.c.	50	3/ 8/31	ragweed	+		
		1932				0.22	c.c.	0							5/22/33	ragweed	±		
		1933				0.06	c.c.	0							3/19/35	ragweed	+		
78	40	1930				0.8	c.c.	75	1933			0.65	c.c.	90	9/13/29	ragweed	++++		
		1931				0.8	c.c.	90							3/14/31	ragweed	+		
		1932				0.8	c.c.	90							3/25/32	ragweed	++		
															8/29/32	ragweed	+		
															9/ 9/33	ragweed	±		
79	16	1929	1.0	c.c.	100	1.0	c.c.	75	1932	1.0	c.c.	100	0.8	c.c.	90	11/19/28	grasses	−	−	++
		1930	0.6	c.c.	100	0.75	c.c.	90	1933	1.0	c.c.	90	0.8	c.c.	100		ragweed	+++		
		1931	0.8	c.c.	100	1.0	c.c.	90	1934	1.0	c.c.	90	0.75	c.c.	100	2/ 8/30	grasses	−	−	+
																	ragweed	±		
																1/17/31	grasses	−	−	−
																	ragweed	−	+	+++
																10/ 4/33	grasses	−	−	−
																	ragweed	−	−	+
																11/21/34	grasses	−	−	−
																	ragweed	−	−	+

PROTOCOL—CONT'D

CASE NUMBER	AGE FIRST SEEN	PRESEASONAL TREATMENT*						PERENNIAL TREATMENT						POLLEN TEST REACTIONS†				
			GRASSES		RAGWEED				GRASSES		RAGWEED							
		POLLEN YEAR	MAXIMUM DOSE INJECTED‡	RELIEF IN PER CENT	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT§		POLLEN YEAR	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT		DATE	POLLEN SEASON	SCR.: DRY POLLEN, 1:50 EXT.	INTR.: COCA, 1:50 EXT.	EYE: DRY POLLEN
80	51	1929			1.05 c.c.	75		1932			0.7 c.c.	75		1/25/29	ragweed	++++		
		1930			1.0 c.c.	75		1933			0.7 c.c.	75		4/ 4/32	ragweed	−	−	+++
		1931			0.8 c.c.	90								10/12/33	ragweed	−	−	++
		Perennial Asthma With Pollen Allergy (Children)																
81	10	1928	1.9 c.c.	90	1.0 c.c.	90		1933	0.85 c.c.	90	0.8 c.c.	100		1/ 7/28	grasses	+++		
		1929	1.5 c.c.	100	0.9 c.c.	100		1934	0.85 c.c.	100	0.85 c.c.	90			ragweed	+++		
		1930	1.5 c.c.	90	0.8 c.c.	75								2/14/30	grasses	+		
		1931	1.0 c.c.	75	0.8 c.c.	75									ragweed	±		
		1932	0.85 c.c.	75	0.8 c.c.	75								2/ 5/32	grasses	−	−	+
															ragweed	−	−	++++
														9/29/33	grasses	−	+	++
															ragweed	−	−	++++
														7/ 3/34	grasses	−	++	+++
															ragweed	−	++	+++
														11/11/34	grasses	−	+	+++
															ragweed	−	+	+++
82	8	1929			1.0 c.c.	100		1932			0.75 c.c.	100		11/ 6/28	ragweed	−	+	+++
		1930			1.0 c.c.	100								10/ 5/30	ragweed	−	−	++
		1931			0.9 c.c.	100								3/ 6/31	ragweed	−	−	+
														3/28/32	ragweed	−	−	+

83	6	1930	1.2	c.c.	50	0.5	c.c.	50							12/24/29	grasses	−	−	−
		1931	1.2	c.c.	50	0.7	c.c.	75								ragweed	+		
		1932	1.0	c.c.	50				1932				0.85	c.c. 90	12/29/30	grasses	−	−	−
									1933	0.95	c.c.	90	0.8	c.c. 90		ragweed	±	+	++
									1934	0.6	c.c.	90	0.8	c.c. 100	1/14/32	grasses	−	−	−
																ragweed	−	−	++
															9/22/33	grasses	−	−	−
																ragweed	−	−	+++
															4/13/35	grasses	−	−	−
																ragweed	±	+++	++++
84	5	1930	1.2	c.c.	90										1/23/30	grasses	−	+	++
		1931	1.0	c.c.	90	0.8	c.c.	75								ragweed	−	−	+
		1932			(T)	0.8	c.c.	75	1933			(T)	0.85	c.c. 75	1/12/31	grasses	−	−	+
									1934			(T)	0.85	c.c. 75		ragweed	−	−	+
															9/30/32	grasses	−	−	−
																ragweed	−	−	++
															10/22/34	grasses	−	−	++
																ragweed	−	−	++
85	5	1930	1.4	c.c.	90	0.9	c.c.	50	1933	0.8	c.c.	0	1.0	c.c. 75	11/30/29	grasses	−	−	+++
		1931	0.7	c.c.	90	0.75	c.c.	0	1934	1.0	c.c.	75	1.0	c.c. 50		ragweed	−	−	++
		1932	1.0	c.c.	50	0.8	c.c.	75							4/16/31	grasses	−	−	+
																ragweed	−	−	+
															10/17/34	grasses	−	−	−
																ragweed	−	−	+
86	6	1928	1.5	c.c.	100										12/19/27	grasses	++		
		1929	1.0	c.c.	90	0.9	c.c.	50								ragweed	−	−	++++
		1930	1.6	c.c.	90	0.65	c.c.	50							1/19/30	grasses	+		
		1931	1.4	c.c.	100	0.7	c.c.	75	1933	1.0	c.c.	75	0.9	c.c. 75		ragweed	−	−	+++
		1932	1.0	c.c.	90	0.7	c.c.	90	1934	1.0	c.c.	100	0.9	c.c. 90	1/24/31	grasses	−	−	+
																ragweed	−	−	+
															3/17/34	grasses	−	−	−
																ragweed	−	−	−
															12/12/34	grasses	−	−	−
																ragweed	−	−	−

PROTOCOL—CONT'D

CASE NUMBER	AGE FIRST SEEN	PRESEASONAL TREATMENT*						PERENNIAL TREATMENT						POLLEN TEST REACTIONS†				
			GRASSES		RAGWEED				GRASSES		RAGWEED							
		POLLEN YEAR	MAXIMUM DOSE INJECTED‡	RELIEF IN PER CENT	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT§		POLLEN YEAR	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT		DATE	POLLEN SEASON	SCR.: DRY POLLEN, 1:50 EXT.	INTR.: COCA, 1:50 EXT.	EYE: DRY POLLEN
87	12	1929	1.4 c.c.	100	0.9 c.c.	90		1933	1.0 c.c.	100	0.5 c.c.	90		10/22/28	grasses	−	−	++++
		1930	1.4 c.c.	100	0.7 c.c.	90		1934	1.0 c.c.	75	0.5 c.c.	90			ragweed	−	+	++++
		1931	1.6 c.c.	100	0.5 c.c.	100								2/17/32	grasses	−	−	+++
		1932	1.0 c.c.	90	0.5 c.c.	90									ragweed	−	−	+++
														8/10/34	grasses	−	−	+
															ragweed	−	++	+++
														12/31/34	grasses	−	+	+++
															ragweed	−	++	+++
88	10	1928			1.15 c.c.	90		1932			0.8 c.c.	90		11/16/27	ragweed	++++		
		1929			1.05 c.c.	100		1933			0.8 c.c.	100		3/16/29	ragweed	±		
		1930			0.9 c.c.	90								7/14/32	ragweed	−	++	+++
		1931			0.85 c.c.	90								3/18/33	ragweed	−	−	+++
89	8	1932			0.5 c.c.	90		1933			0.5 c.c.	75		10/27/31	ragweed	++		
								1934			0.5 c.c.	90		9/18/32	ragweed	±		
														6/29/34	ragweed	±		
90	5	1932	1.0 c.c.	90	0.7 c.c.	90		1933	0.88 c.c.	90	0.6 c.c.	90		6/19/31	grasses	±		
								1934	0.88 c.c.	0	0.6 c.c.	50			ragweed	+		
														10/11/33	grasses	−	−	++
															ragweed	±		
														10/27/34	grasses	−	−	++
															ragweed	−	−	−

91	6	1929				0.8	c.c.	75	1932				0.7	c.c.	90	8/25/28	ragweed	++++		
		1930				0.75	c.c.	100	1933				0.7	c.c.	0	3/19/30	ragweed	+		
		1931				0.75	c.c.	50								1/16/32	ragweed	±		
																9/28/33	ragweed	±		
92	6	1929	1.7	c.c.	75	0.8	c.c.	75	1932	1.0	c.c.	90	0.8	c.c.	75	10/20/28	grasses	+		
		1930	2.0	c.c.	90	0.8	c.c.	100	1933	1.0	c.c.	90	0.8	c.c.	90		ragweed	+		
		1931	1.4	c.c.	100	0.8	c.c.	90	1934	1.0	c.c.	90	0.8	c.c.	90	2/ 3/31	grasses	±	++	
																	ragweed	±		
																3/ 5/32	grasses	−	−	+
																	ragweed	−	−	+++
																10/14/33	grasses	−	++	+++
																	ragweed	−	−	+++
																3/ 2/35	grasses	−	+	++
																	ragweed	−	+	+
93	9	1932	0.8	c.c.	90	0.8	c.c.	50	1933	1.0	c.c.	90	0.85	c.c.	50	2/ 5/32	grasses	−	+	++
									1934	1.0	c.c.	90	0.8	c.c.	75		ragweed	±	++	
																11/24/34	grasses	−	−	−
																	ragweed	−	++	+++
94	10	1930	0.12	c.c.	90	0.4	c.c.	90	1933	1.0	c.c.	100	0.85	c.c.	100	4/16/30	grasses	−	+	+++
		1931	1.3	c.c.	100	0.8	c.c.	90	1934	1.0	c.c.	90	0.95	c.c.	100		ragweed	++		
		1932	1.0	c.c.	90	0.8	c.c.	100								1/18/32	grasses	−	+	++
																	ragweed	±		
																11/16/34	grasses	−	+	++
																	ragweed	−	++	+++
95	6	1931				0.8	c.c.	90	1933				0.85	c.c.	90	8/29/30	ragweed	−	−	++++
		1932				0.8	c.c.	100	1934				0.95	c.c.	75	1/18/32	ragweed	−	−	+++
																11/19/33	ragweed	−	++	+++
																11/23/34	ragweed	−	−	+++
96	7	1928	1.0	c.c.	100	1.0	c.c.	90	1933	1.0	c.c.	100	0.85	c.c.	100	11/ 5/27	grasses	++		
		1929	1.0	c.c.	100	1.0	c.c.	90	1934	1.0	c.c.	100	1.0	c.c.	100		ragweed	++		
		1930	1.5	c.c.	90	0.85	c.c.	75								2/ 8/30	grasses	±		
		1931	1.0	c.c.	100	0.9	c.c.	100									ragweed	±		
		1932	1.0	c.c.	100	0.9	c.c.	90								1/ 9/32	grasses	−	+	+++
																	ragweed	−	+	++
																10/26/34	grasses	−	−	+
																	ragweed	−	−	+++

PROTOCOL—CONT'D

CASE NUMBER	AGE FIRST SEEN	PRESEASONAL TREATMENT*						PERENNIAL TREATMENT						POLLEN TEST REACTIONS†				
			GRASSES			RAGWEED			GRASSES			RAGWEED						
		POLLEN YEAR	MAXIMUM DOSE INJECTED‡	RELIEF IN PER CENT		MAXIMUM DOSE INJECTED	RELIEF IN PER CENT§	POLLEN YEAR	MAXIMUM DOSE INJECTED	RELIEF IN PER CENT		MAXIMUM DOSE INJECTED	RELIEF IN PER CENT	DATE	POLLEN SEASON	SCR.: DRY POLLEN, 1:50 EXT.	INTR.: COCA, 1:50 EXT.	EYE: DRY POLLEN
97	6	1930	0.8 c.c.	75		0.7 c.c.	50	1932	0.8 c.c.	50		0.6 c.c.	75	9/14/29	grasses	++		
		1931	1.0 c.c.	90		0.65 c.c.	75	1933	1.0 c.c.	75		0.6 c.c.	90		ragweed	+++		
								1934	1.0 c.c.	75		0.6 c.c.	90	1/14/31	grasses	−	+	+++
															ragweed	++		
														3/12/32	grasses	−	−	++
															ragweed	−	+	+++
														11/ 3/34	grasses	−	−	+
															ragweed	−	−	+++
98	6	1930	(U) 0.07 c.c.	90		0.14 c.c.	75	1933	(U)0.1 c.c.	100		0.12 c.c.	90	2/11/30	oak	+		
		1931	(U) 0.1 c.c.	90		0.18 c.c.	75	1934	(U)0.1 c.c.	100		0.12 c.c.	90		ragweed	+++		
		1932	(U) 0.11 c.c.	100		0.19 c.c.	90							10/13/33	oak	±		
															ragweed	+		
														1/14/35	oak	−	+	+++
															ragweed	±	+++	
99	9	1932	0.85 c.c.	90		0.9 c.c.	90	1933	0.9 c.c.	75		0.7 c.c.	90	10/26/31	grasses	+		
								1934	1.0 c.c.	75		0.8 c.c.	100		ragweed	+		
														2/ 2/33	grasses	±		
															ragweed	−	+	++
														10/ 5/33	grasses	−	−	−
															ragweed	−	+	++
														10/30/34	grasses	−	−	−
															ragweed	±	+	++

100	6	1930	0.8	c.c.	90	0.8	c.c.	0	1932	0.85	c.c.	100	0.7	c.c.	90	11/14/29	grasses	+		
		1931	1.0	c.c.	90	0.75	c.c.	90	1933	0.9	c.c.	100	0.7	c.c.	0		ragweed	++		
									1934	1.0	c.c.	100	0.9	c.c.	90	1/11/31	grasses	−	−	+
																	ragweed	−	++	+++
																2/27/32	grasses	−	−	−
																	ragweed	−	+	++
																10/27/34	grasses	−	−	−
																	ragweed	−	−	−

*A course of preseasonal treatment includes injections given prior to and during the pollinating season.

†Only the initial pollen test reactions and the subsequent changes occurring with any method of testing are recorded. The original number of tests made was over 1000 (counting all methods of testing with the pollens of a particular season as one test. For details refer to "Material and Methods"), and the number of tests recorded in the protocol is 531. Scr. = scratch test; intr. = intradermal test; and eye = pure dry natural pollen ophthalmic test. For classification and interpretation of the scratch and intradermal (Cooke) tests see Reference 25 and, for the dry pollen eye test see Reference 18.

‡Maximum dose of pollen injected in terms of 1:50 dilution.

§Due to the variation in the pollen concentration of the air from year to year, the relief from symptoms of pollen allergy must necessarily be conservatively recorded. Relief in terms of percentage was adopted merely as a matter of convenience of record, and so the percentage figures in this series can be used only as a means of comparison by other workers when their figures correspond to the following classification: 50 per cent, definite relief; 75 per cent, marked relief; 90 per cent, almost complete relief; 100 per cent, complete absence of all symptoms of pollen allergy; any grading less than the foregoing percentages is classified as 0 per cent. (A) Dose represents an extract containing equal parts of ash and oak pollen. (B) Perennial treatment discontinued after Sept. 16, 1932. See Table III. (C) Plantain 0.2 c.c. added to grass treatment commencing with 1931. (D) Plantain 0.15 c.c. added to grass treatment commencing with 1931. (E) Perennial treatment discontinued at end of pollen season. (F) Perennial treatment discontinued Sept. 2, 1931. See Table III. (G) Perennial treatment discontinued at end of pollen season. (H) Perennial treatment discontinued by patient. (I) No treatment in 1930, had only mild hay fever, but in 1931 the hay fever was severe. (J) Coseasonal grass treatment. (K) Omitted treatment in 1930. Hay fever and asthma severe. (L) Perennial treatment discontinued at end of pollen season because of "irritation" general reactions. See Table III on general reactions. (M) Hickory pollen. (N) Omitted treatment in 1930. Hay fever and asthma severe. (O) Oak pollen. (P) Coseasonal intradermal therapy. Maximum dose of pollen 1:500 0.03 c.c. Negligible grass symptoms first appeared in pollen season of 1932. (Q) Perennial treatment discontinued at end of pollen season because of general "irritation" reaction. See Table III. (R) Perennial treatment discontinued by patient because of major surgical operation. (S) Also suffered a severe delayed eye reaction lasting three days. (T) No grass treatment administered. Free from symptoms of pollen allergy during 1932 and 1933 but had mild symptoms during 1934. (U) Oak pollen.

The figures in Table I were obtained from the protocol. It shows the number of courses of pollen treatment administered to 100 selected patients during the total period of treatment with the preseasonal and perennial methods.

TABLE I

THE TOTAL NUMBER OF COURSES OF POLLEN TREATMENT ADMINISTERED TO 138 CASES (COUNTING EACH SEASON OF EACH PATIENT AS A SEPARATE CASE) WITH THE PRESEASONAL AND PERENNIAL METHODS

DIAGNOSIS*	RAGWEED	GRASSES	PLANTAIN	TREES	TOTAL
Preseasonal Treatment (Adults)					
Hay fever	42	43	4	3	92
P. A. and H. F.	58	36	0	1	95
Per. A. and H. F.	48	16	0	0	64
Total	148	95	4	4	251
Preseasonal Treatment (Children)					
Hay fever	20	16	0	0	36
P. A. and H. F.	20	11	0	1	32
Per. A. and H. F.	54	40	0	3	97
Total	94	67	0	4	165
Grand Total	242	162	4	8	416
Perennial Treatment (Adults)					
Hay fever	31	22	4	0	57
P. A. and H. F.	27	11	0	1	39
Per. A. and H. F.	33	16	0	0	49
Total	91	49	4	1	145
Perennial Treatment (Children)					
Hay fever	14	9	0	0	23
P. A. and H. F.	19	10	0	3	32
Per. A. and H. F.	43	29	0	2	74
Total	76	48	0	5	129
Grand Total	167	97	4	6	274

*P. A. = pollen asthma; H. F. = hay fever; Per. A. = Perennial asthma.

The average period of treatment per patient with the preseasonal method was three years. The number of courses of treatment administered to adults was 251 and to children 165, or a total number of 416 (Table I).

The average period of treatment per patient with the perennial method was two years. The number of courses of treatment administered to adults was 145 and to children 129, or a total number of 274 (Table I).

With the perennial method, 11 adults or 11 per cent of the entire series of 100 patients, or 18 per cent of the adult series, the treatment was discontinued for the following reasons. In two patients (Cases 1 and 15, protocol) unpleasant general reactions occurred early in the treatment along with a lack of tolerance to the injections at biweekly

intervals. In the remaining nine patients (Cases 9, 22, 37, 42, 44, 45, 50, 65 and 68, protocol), after one to three years, treatment was discontinued because of no relief or a marked decrease in relief or because of frequent general (constitutional) reactions. The offending pollens in these 11 adults were: trees, 1; grasses, 3; and ragweed, 7.

It is of interest to note that with the perennial treatment the total number of courses administered to adults and children were approximately the same, yet in no child was perennial treatment discontinued for causes compelling its discontinuance in the 11 adults mentioned.

Table II shows a summary of the 100 patients with reference to the corresponding results of treatment obtained with the preseasonal and perennial methods. The results are compared in terms of increasing, decreasing, and stationary relief or failure of relief from symptoms of pollen allergy.

Table II shows that in about 55 per cent of the adults with pollen allergy under preseasonal treatment the relief obtained remained stationary, whereas 34 per cent showed a tendency to increasing relief from year to year. In children, stationary relief occurred in about 69 per cent and the tendency to increasing relief in only 19 per cent. Thus, it appears evident that in children the maximum results from preseasonal treatment are obtained sooner than in adults by 14 per cent.

Under consecutive courses of treatment, children show a greater trend to decreasing relief than adults, the incidence being 9.7 and 2.6 per cent respectively, or a ratio of 4:1.

After patients have been under preseasonal treatment one or more years to terminate finally with failure of relief, the incidences of such occurrences in adults and children were 8 and 1.6 per cent, respectively, or a ratio of 5:1.

With the perennial method, all the aforementioned differences in results (with the exception of "failures of relief") between adults and children do not occur. The failures under the perennial method (and this applies only to the last year of treatment) in adults and children were 16 and 6.5 per cent, respectively, or a ratio of 2.5:1. The reduction in the ratio of failures from 5:1 with the preseasonal method to 2.5:1 with the perennial method is due to the fact that the percentage of failures in children under perennial treatment rose four times and in adults only two times over the incidence of failures with the preseasonal treatment.

A comparison between the perennial and the preseasonal methods of treatment in adults shows that the relief with the perennial method remained stationary in 58 per cent of the cases as compared with 55.2 per cent under preseasonal treatment. With the perennial method there occurred increased relief in 12 per cent of the cases as compared with increasing relief in 34.2 per cent under preseasonal treatment. Of

TABLE II

A SUMMARY OF 138 CASES WITH POLLEN ALLERGY (COUNTING EACH SEASON OF EACH PATIENT AS A SEPARATE CASE; ACTUAL NUMBER OF PATIENTS, 100) WITH REFERENCE TO THE COMPARATIVE RESULTS OBTAINED DURING THE TOTAL PERIOD OF TREATMENT WITH THE PRESEASONAL AND PERENNIAL METHODS

	NUMBER OF CASES*	DIAGNOSIS†	PRESEASONAL TREATMENT — PROGRESS OF RELIEF — NUMBER: INCREASING	DECREASING	STATIONARY‡	FAILURES§	PRESEASONAL TREATMENT — PROGRESS OF RELIEF — PERCENTAGE‖: INCREASING	DECREASING	STATIONARY	FAILURES	PERENNIAL TREATMENT — PROGRESS OF RELIEF** — NUMBER: INCREASED	DECREASED	STATIONARY	FAILURES¶	PERENNIAL TREATMENT — PROGRESS OF RELIEF** — PERCENTAGE: INCREASED	DECREASED	STATIONARY	FAILURES
Adults																		
	29 (23)	H. F.	8	1	19	1	27.5	3.5	65.5	3.5	3	3	18	5	10.5	10.5	62.0	17.0
	23 (19)	P. A. and H. F.	10	0	10	3	43.5	0	43.5	13.0	3	4	12	4	13.0	17.5	52.0	17.5
	24 (18)	Per. A.; P. Al.	8	1	13	2	33.5	4.0	54.0	8.5	3	4	14	3	12.5	16.5	58.5	12.5
Total	76 (60)		26	2	42	6	34.2	2.6	55.2	8.0	9	11	44	12	12.0	14.0	58.0	16.0
Children																		
	15 (11)	H. F.	2	1	12	0	13.0	7.0	80.0	0	1	3	10	1	7.0	20.0	66.0	7.0
	13 (9)	P. A. and H. F.	2	1	9	1	15.0	8.0	69.0	8.0	2	2	8	1	15.0	15.0	62.0	8.0
	34 (20)	Per. A.; P. Al.	8	4	22	0	23.0	12.0	65.0	0	6	6	20	2	17.5	17.5	59.0	6.0
Total	62 (40)		12	6	43	1	19.3	9.7	69.4	1.6	9	11	38	4	14.5	17.7	61.3	6.5
Grand Total	138 (100)		38	8	85	7	27.5	5.8	61.6	5.1	18	22	82	16	13.0	15.9	59.5	11.6

*The figures to the right of the number of cases represent the actual number of patients.

†H. F. = hay fever; P. A. = pollen asthma; Per. A. and P. Al. = perennial asthma and pollen allergy.

‡Cases under preseasonal treatment for only one year are included here and are about equally divided between adults and children, numbering 17 and 15, respectively. The actual number of patients was 15 adults and 10 children.

‖All percentage figures are based on 138 cases. For statistical and practical purposes 90 and 100 per cent relief were regarded as the same.

§Failure of relief; in patients under preseasonal treatment more than one year, apply to the pollen season preceding the institution of perennial therapy.

**Progress of relief with perennial treatment refers to the results obtained as compared with those obtained on the same patients who previously were under preseasonal treatment. For example, "stationary relief" under perennial treatment implies that the percentage of relief is no different from that previously obtained with the preseasonal method, and when the case is under perennial treatment more than one year, (¶) "failure of relief" refers to the last year of treatment.

note under perennial treatment is the decreased relief occurring in 14 per cent of the cases as compared with the decreasing relief in only 2.6 per cent of the cases under preseasonal treatment. Failure of relief rose to 16 per cent of the cases under perennial treatment as compared with 8 per cent under preseasonal therapy, a ratio increase of 2:1.

A comparison between the perennial and the preseasonal methods of treatment in children shows that the relief with the perennial method remained stationary in 61.3 per cent of the cases as compared with 69.4 per cent under preseasonal treatment. Increased relief with the perennial method occurred in 14.5 per cent of the cases as compared with 19.3 per cent under preseasonal therapy. Decreased relief with the perennial method occurred in 17.7 per cent of the cases as compared with 9.7 per cent under preseasonal treatment, a fact worthy of note. Failure of relief under perennial treatment rose to 6.5 per cent as compared with 1.6 per cent under preseasonal treatment, or a ratio of 4:1.

A comparison between the perennial and the preseasonal methods of treatment of the total number of adults and children shows that the relief with the perennial method remained stationary in 59.5 per cent as compared to 61.6 per cent under preseasonal treatment. Increased relief with the perennial method occurred in 13 per cent of the cases as compared with 27.5 per cent under preseasonal therapy. Decreased relief with the perennial method occurred in 15.9 per cent as compared with 5.8 per cent under preseasonal treatment, a ratio of almost 3:1. Failure of relief with the perennial method occurred in 11.6 per cent of the cases as compared with 5.1 per cent under preseasonal, a ratio of about 2:1. These figures are all the more significant in view of the fact that the perennial method of treatment was tried on selected patients with pollen allergy, almost all of whom did well on preseasonal treatment, ranging from one to twelve years.

Of special interest are the 16 cases with failure of relief from pollen allergy under perennial treatment. In two of these cases (No. 1, grasses; No. 15, oak and ash; adults, see protocol) treatment was discontinued because of unpleasant general reactions occurring early in the treatment along with their inability to tolerate the biweekly interval between injections. Failure of relief in six other cases occurred at the end of one year of treatment (Cases 42, 44, 50, 52 [adults], 72 [child], ragweed; and 69 [adult], grasses); in another six cases failure of relief occurred at the end of two years (Cases 8, 9, 32, 75 [adults], 91 [child], ragweed; and 90 [child], grasses); in the remaining two cases failure of relief occurred at the end of three years (Cases 22 [adult] and 61 [child], ragweed).

The following three cases with ragweed sensitivity showed failure of relief during years other than the last year of perennial treatment and for this reason were not included in the foregoing group of failures. At the end of the first year of perennial treatment, two cases (Nos. 41

and 64, protocol) showed failure of relief but at the end of the second year were relieved, 50 and 100 per cent respectively. Another case (No. 100) showed failure of relief during the second year but 90 per cent relief at the end of the first and third years of perennial treatment.

Four (Cases 4 [grasses], 51, 77 [adults] and 60 [child], ragweed) of the seven cases under preseasonal treatment, in which failure of relief of pollen allergy occurred during the last year of treatment, were definitely relieved with perennial treatment. The fifth case (No. 52, [adult], ragweed) was not relieved with perennial treatment. The sixth case (No. 69 [adult], grasses) did well with preseasonal treatment but had failure of relief the first year on perennial treatment and continued to have no relief the following year when returned to the preseasonal method. The remaining case (No. 44 [adult], ragweed) also did well on preseasonal treatment and had failure of relief the first year on the perennial method and continued to have no relief the subsequent two years on preseasonal treatment.

Thus, four of the seven cases ending in failure of relief under preseasonal treatment were definitely relieved by the perennial method, while 13 of the 16 cases of failure with the perennial treatment did well with the preseasonal method.

It is of further interest to note that in the same patient during the same year a failure of relief can occur with the perennial method with one pollen season and a good result obtained with a different pollen season. Whether this clinical observation occurs more frequently with the perennial than it does with the preseasonal method cannot be determined from this study, because it is comprised of a selected group of patients. No patients sensitive to early and late pollens had failure of relief to both seasons with either method.

It appears quite evident that all the foregoing data do not substantiate the claims advanced regarding the superiority of the perennial over the preseasonal method of treatment of pollen allergy. Moreover, the reported statements that perennial therapy offers a promise of permanent cure were not supported by convincing clinical evidence. As a matter of fact, from a careful analysis of the clinical evidence at hand enthusiastic offers and promises of speedier permanent cures via perennial therapy seem, for the present, premature and unwarranted. The promise of additional failures in therapy can be fulfilled if the perennial method of pollen treatment is employed to the exclusion of the standard preseasonal treatment. The best that can be said in favor of perennial therapy, in view of the hazards involved, is that it should be regarded as another form of pollen treatment to be administered only by qualified allergists on specially selected cases.

GENERAL (CONSTITUTIONAL) REACTIONS

Statistics referring to the frequency, severity, type, and duration of general reactions reported in this series of selected cases are of importance only when the general reactions occurring with the preseasonal and perennial methods of treatment are compared. The general reactions occurring in this series of cases were manifested by the following symptoms: asthma, spasmodic or continual cough, hay fever, vasomotor rhinitis, wheezing spells, urticaria, edema of the eyelids, dizziness, headache, and generalized drawing sensation of the skin. All these symptoms were readily relieved or controlled by the injection of epinephrine hydrochloride (1:1,000 solution) and the application of a tourniquet over the site of the injection. The reactions were described as immediate, accelerated, delayed, and irritative (defined in the footnotes of Table III). The degree of a general reaction was described as severe, moderate, or mild.

The total number of injections administered to adults during 251 courses of preseasonal treatment was 9,327. The total number of general reactions encountered during preseasonal treatment was 28, or one to 333 injections. The total number of injections administered during 145 courses of perennial treatment was 3,668. The number of general reactions encountered during perennial treatment was 35, or one to 105 injections.

The total number of injections administered to children during 165 courses of preseasonal treatment was 6,222. The total number of general reactions encountered during preseasonal treatment was 8, or one to 777 injections. The total number of injections administered during 129 courses of perennial treatment was 3,309. The number of general reactions encountered during perennial treatment was 4, or one to 827 injections.

The combined total number of injections administered to 138 adults and children (counting each pollen season of each patient as a separate case) during 416 preseasonal courses of treatment was 15,549. Thirty-six general reactions were encountered, or a ratio of one to 431 injections.

The combined total number of injections administered to 138 adults and children during 274 courses of perennial treatment (one year of perennial treatment constituting one course) was 6,977. Thirty-nine general reactions were encountered, or a ratio of one reaction to 178 injections. These comparative figures become more impressive when one takes into consideration the knowledge concerning the tolerance of the patient to pollen dosage gained during preseasonal treatment. Of further importance is the fact that with the perennial treatment the injections were usually given at intervals of two weeks and during the pollinating season frequently at weekly intervals; and, that 20 of the 39 general reactions occurred with a dose of pollen extract lower than previous maximum tolerance dosage.

TABLE III

GENERAL (CONSTITUTIONAL) REACTIONS OCCURRING IN THIRTY-ONE PATIENTS WITH POLLEN ALLERGY DURING TREATMENT WITH EITHER THE PRESEASONAL OR THE PERENNIAL METHODS, OR BOTH

	PRESEASONAL TREATMENT				PERENNIAL TREATMENT			
				GENERAL REACTIONS			GENERAL REACTIONS	
CASE NUMBER*	YEAR BEGUN AND NUMBER OF YEARS' TREATMENT	POLLEN INJECTED†	YEAR	REACTION DOSE‡ / DEGREE OF REACTION§	YEAR BEGUN‖ AND NUMBER OF YEARS' TREATMENT	YEAR	REACTION DOSE‡	DEGREE OF REACTION§
				Adults				
1	1932 3	O			1933 1/3	1932	0.6 0.4 0.3 0.2	c.c. AM c.c. AE c.c. AM c.c. AE
4	1932 1	G			1933 2	1932	0.005	c.c. IE
8	1930 3	R	1932	¶0.34	1933 2			
9	1930 2	R			1932 3	1932	0.08 0.08 0.08 0.07 0.06	c.c. DM c.c. DE c.c. DE c.c. DE c.c. DE
						1933	¶0.04	c.c. AS
						1934	0.03	c.c. RE
12	1928 4	R	1928	0.03 c.c. AM	1932 3	1933	¶0.1	c.c. AE
13	1931 1	R			1932 1	1932	0.45	c.c. IM
15	1930 3	G			1931 1/12	1931	0.4	c.c. AS
16	1931 3	G	1933	¶0.1 c.c. AM ¶0.06 c.c. IE	1934 1	1934	0.03	c.c. IE
18	1930 3	G			1933 1	1932 1933	0.03 0.02 0.01	c.c. IE c.c. AM c.c. IE
19	1926 7	G	1932	0.65 c.c. IM	1933 2	1932 1933	0.6 0.55 0.28	c.c. AE c.c. IM c.c. AE
21	1929 3	R	1929	¶0.8 c.c. IE	1933 3			
22	1931 1	R			1932 3	1934	0.08	c.c. RM
36	1929 3	R	1929 1931	¶0.9 c.c. DM 0.7 c.c. DE	1932 2			
38	1920 12	G	1922 1923	0.4 c.c. DM ¶1.8 c.c. AM ¶1.4 c.c. DM ¶0.4 c.c. AE	1933 2	1932	0.028	c.c. IM
			1924	0.12 c.c. AE				
			1925	1.1 c.c. AE				
			1927	¶0.48 c.c. IM				
			1928	¶0.7 c.c. AM				
			1929	¶0.4 c.c. AM ¶0.2 c.c. AE				
			1931	¶0.6 c.c. IE				

TABLE III—CONT'D

CASE NUMBER*	PRESEASONAL TREATMENT					PERENNIAL TREATMENT			
	YEAR BEGUN AND NUMBER OF YEARS' TREATMENT	POLLEN INJECTED†	YEAR	GENERAL REACTIONS		YEAR BEGUN‖ AND NUMBER OF YEARS' TREATMENT	YEAR	GENERAL REACTIONS	
				REACTION DOSE‡	DEGREE OF REACTION§			REACTION DOSE‡	DEGREE OF REACTION§
40	1933 1	R	1933	0.22 c.c.	DE	1934 1			
42	1931 3	R	1933	¶1.0 c.c. ¶0.9 c.c.	AE DE	1932 1	1932	¶0.7 c.c.	AM
44	1926 8	R	1933	¶0.5 c.c.	IM	1932 1	1932	¶0.5 c.c.	IS
45	1930 4	G				1933 1	1932	1.0 c.c.	RM
46	1932 1	G				1933 2	1933	0.75 c.c.	RM
50	1929 5	R	1929 1930 1931	0.44 c.c. 0.4 c.c. ¶0.34 c.c.	DE IM IE	1932 1	1932	0.26 c.c. ¶0.22 c.c.	IM IM
51	1927 5	R				1932 3	1932	¶0.15 c.c.	AM
53	1923 9	R				1932 3	1932	0.6 c.c.	IM
65	1923 11	R				1932 1	1932	0.3 c.c.	RM
71	1931 1	G				1932 3	1934	1.0 c.c.	IM
72	1929 5	R	1933	0.26 c.c. 0.26 c.c.	IE IE	1932 1	1932	0.6 c.c.	AM
				Children					
27	1932 1	G				1933 2	1933	0.12 c.c.	DM
28	1931 2	G	1931	0.008 c.c. 0.016 c.c. 0.02 c.c. 0.024 c.c.	AE AE AE AE	1933 1			
29	1928 5	R	1929 1932	0.42 c.c. 0.1 c.c.	DE DE	1933 1			
32	1931 2	G				1933 2	1933	0.34 c.c. ¶0.4 c.c.	AE DE
93	1932 1	R				1933 2	1933	¶0.8 c.c.	AM
97	1930 2	R	1930	0.65 c.c. 0.65 c.c.	IE IE	1932 3			

*Cases 1 to 36, inclusive, had hay fever; 38 to 53 had pollen asthma and hay fever; and 65 to 97, perennial asthma and pollen allergy.

†O = oak and ash; G = grasses; R = ragweed. The maximum doses injected can be obtained from the protocol.

‡1:50 dilution of pollen extract.

§The severity or degree of general reactions is classified as follows: S = severe; M = moderate; and E = mild. The time of occurrence of a general reaction is designated as, I = immediate reaction, occurs from five to thirty minutes after an injection of pollen; A = accelerated reaction, sets in from one-half to three hours after an injection; D = delayed reaction, sets in from three to twenty-four hours after an injection; R = irritative reaction, indicates symptoms of either bronchial or nasal allergy or both more or less continual over a period of at least one month with no definite time relationship to the injections themselves. These irritative symptoms clear up after perennial treatment is discontinued.

‖The pollen year for which the patient is being prepared.

¶General reaction occurring during pollinating season.

Table III shows the essential data concerning general reactions occurring in 31 cases with pollen allergy during treatment with either or both the preseasonal or perennial methods.

Fifteen patients had general reactions with preseasonal treatment (Table III). In terms of 138 cases and 416 courses of preseasonal treatment (Table I), the percentage of patients with general reactions is 10.8 and 3.6 respectively. Eight of these 15 patients also experienced general reactions during perennial treatment. In addition to these 8 patients, 16 others had general reactions only during perennial treatment, making a total of 24 patients (Table III). In terms of 138 cases and 274 courses of perennial treatment (Table I), the percentage of patients with general reactions is 17.4 and 8.7 respectively. Thus, with the perennial method the number of patients with general reactions is one and one-half times greater than the number occurring with preseasonal treatment.

Of the 138 cases treated, 76 were adults and 62 were children. The adults and children received 251 and 165 courses of preseasonal treatment respectively (Table I). Of the 15 patients with general reactions occurring during preseasonal treatment, 12 were adults and 3 were children. In terms of 76 adults and 251 courses of treatment, the percentage of adults with general reactions was 15.8 and 4.8 respectively. In terms of 62 children and 165 courses of treatment, the percentage of children with general reactions was 4.8 and 1.8 respectively. Thus, with the preseasonal method, about three and one-half times as many adults had general reactions as children.

The adults and children received 145 and 129 courses of perennial treatment respectively (Table I). Of the 24 patients with general reactions during perennial treatment, 21 were adults and 3, children. In terms of 76 adults and 145 courses of treatment, the percentage of adults with general reactions was 27.6 and 14.5 respectively. In terms of 62 children and 129 courses of treatment, the percentage of children with general reactions was 4.8 and 2.3 respectively. Thus, with perennial treatment five and one-half times as many adults had general reactions as children.

The incidence of adults with general reactions rose from 15.8 per cent with the preseasonal to 27.6 per cent with the perennial method. In other words, about twice as many adults experienced general reactions under perennial as compared with preseasonal treatment; whereas the incidence of children with general reactions with both methods of treatment remained unchanged at 4.8 per cent.

The total number of cases encountering general reactions during preseasonal or perennial treatment or both, was 31 (Table III). These patients received a total of 117 courses of preseasonal treatment and 53½ courses of perennial treatment (protocol). Thirty-six general reactions occurred with the preseasonal method, or a ratio of one to

every 3.2 courses. Thirty-nine general reactions occurred with the perennial method, or a ratio of one to every 1.3 courses. Thus, with the perennial method general reactions occurred about two and one-half times more frequently than with the preseasonal method.

With the preseasonal treatment none of the patients encountered an irritative or a severe general reaction, either immediate, accelerated, or delayed. Of the 36 general reactions recorded (Table III), 36 per cent were immediate, 38 per cent were accelerated, and 25 per cent were delayed. Of the 39 general reactions encountered during perennial treatment, there were three severe (one immediate and two accelerated) and a larger percentage of moderate, immediate and accelerated reactions than encountered with the preseasonal method. With the perennial method the general reactions recorded were 31 per cent immediate, 38 per cent accelerated, 18 per cent delayed, and 13 per cent irritative.

Thus, the immediate general reaction with the perennial method dropped to 31 per cent from 36 per cent with the preseasonal method. The delayed general reaction with the perennial method dropped to 18 per cent from 25 per cent with the preseasonal method. The accelerated general reaction showed no appreciable change with either method of treatment, but the irritative general reaction rose from 0 per cent with the preseasonal to 13 per cent with the perennial method. The latter group of reactions is more damaging and more troublesome to the patient than any of the others experienced in this series. Because of its continual nature, the danger of causing organic tissue changes must be entertained. For this reason, perennial treatment was discontinued in most of the patients exhibiting this reaction. Moreover, in a few of the patients with the irritative general reaction, the continuation of perennial treatment was made possible when the interval between injections was reduced to one week and the dose of pollen extract lowered. Such a modification of the perennial treatment eliminates one of the main reasons for its existence, for such a modification cannot then be classified as "real" perennial treatment.

Eight of the 31 patients with general reactions were also treated with other pollens which did not cause general reactions. Of these, four (Cases 8, 42, 93 and 97) also received grasses, three (Cases 28, 32 and 71) ragweed, and the remaining one (Case 46) received hickory pollen extract.

It can be seen from Table III that general reactions may make their appearance during any year of treatment with both the preseasonal and the perennial methods, but with the latter general reactions make their appearance sooner than with the preseasonal method.

Of the 36 general reactions encountered during preseasonal therapy, 14 or 39 per cent occurred during the pollinating season. The top dose of pollen injected prior to the onset of the season in a majority of the cases was usually carried through pollination at weekly intervals.

Of the 39 general reactions encountered during perennial therapy, eight reactions or 20 per cent occurred during the pollinating season. This lower incidence of general reactions is explained by the facts that the top dose of pollen extract in many of the patients on perennial therapy was smaller than the top dose they received under the preseasonal method, the time interval between injections was frequently reduced to one week, and also the occurrence of general reactions encountered outside the pollen season necessitated a further reduction in the pollen dosage.

In this series, general reactions occurred with doses ranging from 0.05 c.c. of 1:500 to 1.8 c.c. of a 1:50 dilution of pollen extract.

The relation of the general reaction to the pollen test reaction is of interest. Of the 31 patients in whom general reactions occurred during either preseasonal or perennial treatment or both, the scratch tests showed positive reactions in 26 at the time they first came under observation (Table III and protocol). When the general reactions occurred, the scratch test reactions to pollen in all these 26 cases were still positive (although reduced in size in many instances) with the exception of two cases. In one of these two (Case 65) the intradermal test (1:50 dilution) showed a one-plus reaction and the dry pollen eye test, a two-plus reaction; while in the other (Case 29, year 1932) the intradermal test showed a two-plus and the dry pollen eye test, a three-plus reaction.

In two of the remaining five patients (Cases 1 and 42) the scratch and intradermal tests were negative at the time they first came under observation, and the dry pollen eye tests were positive. All these reactions were unchanged at the time of the occurrence of the general reaction.

In the third case (No. 36) the intradermal test showed a one-plus and the dry pollen eye test a two-plus reaction when first observed. These reactions remained unchanged two years later when the first general reaction occurred. At the end of the fourth year when the second general reaction occurred, only the dry pollen eye tests showed positive reactions (two-plus). In the remaining two cases (Nos. 45 and 71) the cutaneous and dry pollen eye tests showed negative reactions when first observed. The test reactions remained unchanged at the time of the general reactions.

Thus, it is quite evident that general reactions may occur in the absence of positive cutaneous reactions (scratch and intradermal) and even in the absence of a positive dry pollen eye reaction. General reactions, however, occur more frequently in patients showing positive than in those showing negative cutaneous reactions. A reduction in the size or the eradication of a positive skin reaction as a result of pollen treatment is no evidence of immunity against a general reaction. Of clinical and academic interest is the occurrence of general reactions in patients remaining persistently negative to all tests including the dry pollen eye tests.

In view of all the foregoing data, it appears definite that general reactions are more disturbing and occur more frequently with the perennial than with the preseasonal method of pollen treatment.

The relationship between the percentage of relief from symptoms of pollen allergy and the pollen test reactions (scratch, intradermal, and dry pollen eye technics) in the patients under treatment with the preseasonal and perennial methods is of much interest. This phase of allergy has raised many points of controversial nature. Many important findings will be brought forth in a future communication.

COMMENT

The true value of the perennial treatment of pollen allergy and its supposed superiority over the preseasonal method have not been settled, despite favorable reports of the majority of the communications in the literature on this subject. One cannot conceive of settling such an important question from the relatively small number of cases thus far reported. These are indeed surprisingly small when one takes into consideration that during the last six years the perennial treatment has been actively employed. It seems reasonable to assume that the unreported cases on perennial treatment must loom large, and among them there undoubtedly exists an appreciable number of patients in whom the results did not measure up to its presently accepted reputation.

When one reads the literature on perennial treatment, the impression is gained that the hope of permanent cure can be obtained with this method of treatment. Walker[20] reported a group of patients treated preseasonally during the years 1918 to 1922 inclusive, in whom 20 per cent have been free from symptoms without treatment for years. In another communication Walker[21] reported a series of 100 cures. Rackemann[22] reported an incidence of 6.3 per cent cures on preseasonal treatment in ragweed and 7 per cent in timothy hay fever. Permanent relief was obtained after one to seven years of treatment. Thommen[15] reported an incidence of 6.8 per cent. The cases with spontaneous cures are well known, but the incidence of occurrence is not known. The question as to whether or not a cure can be regarded as a clinical or immunologic phenomenon is not pertinent to this subject. The question of immediate importance is whether or not the percentage of cures with perennial treatment is substantially raised above the level reported for preseasonal treatment. Thus far, there are no obtainable figures in the literature to answer this question. The statement that perennial treatment offers "the promise of a permanent cure" appears in almost every paper on the subject. No scientific evidence has thus far been produced which can prophesy or at least indicate when a cure with any method of treatment has been established. My past experiences corroborate the findings in the series of cases here reported that the eradication of all reactions, including the dry pollen eye reaction, is by no means an indication that

a cure has been effected. If the argument be raised that the induction of negative cutaneous and ophthalmic reactions in man has brought about sufficient alteration of the allergic state to warrant the statement that such a patient will escape the symptoms of pollen allergy, then what alteration exists in the untreated patient exhibiting negative cutaneous and dry pollen eye reactions with a positive history of pollen intolerance? Can one infer such a patient is not suffering from pollen allergy in spite of the fact that treatment against the offending substance brings about complete relief after all other methods of treatment have failed? A study of the protocol of my series of cases and unpublished data indicate that the criteria as to whether a patient is permanently cured from allergy does not rest entirely, if at all, upon the eradication of positive cutaneous, ophthalmic, and even passive transfer reactions.

For a few years following 1920, Cooke, Vander Veer and Spain[7] could not practice the perennial treatment principally because of unstable extracts (none holding their potency for more than a few months) and the risk of unpleasant constitutional reactions. With the introduction of Coca's solution for the extraction of pollen, they obtained a stable extract, which removed the chief objection to the monthly treatments. Brown[4] soon discovered that general (constitutional) reactions occurred upon changing from an old (Coca) extract to a new one. This worker claimed to have overcome this difficulty satisfactorily by his method of mixing old and new extracts. He[23] likewise rediscovered that 50 per cent glycerolated pollen solutions maintain their potency for years, and concluded they have added the last link in the perennial treatment. Cooke and his coworkers[24] confirmed the findings of previous workers that the active antigenic substances in pollen were protein in nature, and a new system of standardizing pollen extracts was established. Nevertheless, general reactions with perennial treatment continued to maintain an uncomfortably high incidence. In this study the problem of deterioration of pollen extracts was solved by using Coca extracts freshly prepared at least every two months, and the incidence of general reactions with the perennial method was higher than that with the preseasonal. It seems quite evident that the major cause of an increased incidence of general reactions with perennial treatment, no matter how carefully and conservatively the treatment is administered, does not rest with the method of preparation of pollen extracts.

It has been explained that a certain group of patients under perennial treatment experienced a type of general reaction manifested by symptoms of a continual character extending over a period of months. Following the discontinuance of treatment the unfavorable symptoms eventually cleared. This reaction was designated with the term "irritative general reaction." In this study the irritative general reaction occurred only with perennial therapy.

The clinical facts obtained in this study clearly indicate that standardization of pollen treatment cannot be accomplished. Even if the chemical formula of pollen were known, the problem of standardization of treatment would still remain unsolved because there still is no accurate nor reliable means of gaging in advance the protection dose of pollen to be administered to a given patient.

The impression should not be gained that I am unalterably opposed to the continuation of the perennial treatment of pollen allergy. This study merely emphasizes the warning concerning its limitations, recognition of the dangers involved, and the restriction of its use, for the present, to trained workers in allergy.

CONCLUSIONS

1. One hundred selected patients (60 adults and 40 children) with pollen allergy were under preseasonal treatment for an average of three years for each patient. All these patients with a few exceptions were either definitely improved or entirely relieved of hay fever and pollen asthma. This group of patients was placed under perennial treatment and received an average of two years' treatment for each patient.

The pollen sensitivities in the 100 cases were: trees, 4; grasses, 50; and ragweed, 84; totaling 138 cases, 76 adults and 62 children (counting each season of each patient as a separate case). The following percentage figures are based on 138 cases unless otherwise stated.

2. With both methods of treatment, children demonstrate the ability to accept and require as large doses of pollen extracts as adults, or larger doses. Under perennial treatment, however, children and adults in a large number of cases could not maintain, nor did they always require, the maximum dose of pollen extract administered under preseasonal treatment.

3. With the preseasonal method, general reactions occurred about two and one-third times more frequently in adults than in children, while with the perennial method the ratio of general reactions was about 8:1. Therefore, the problem of general reactions with both the preseasonal and the perennial methods of treatment is one which mainly affects adults.

4. General reactions may make their appearance during any year of treatment with both the preseasonal and the perennial methods. With the latter method and usually with reduced top pollen dosage, general reactions make their appearance sooner than with the preseasonal method.

5. With preseasonal treatment the incidence of adults and children with general reactions occurred in a ratio of about 3:1; and with the perennial treatment, the ratio was about 5½:1.

6. Under perennial treatment the general reactions ranging from immediate to delayed were more severe, and in a certain group of patients the symptoms were of a continual character extending over a

period of months. The latter general reaction was termed "irritative," occurring in 8.3 per cent of the adult series. Following the discontinuance of perennial treatment the symptoms of an irritative general reaction eventually cleared. The irritative general reaction assumes importance lest failure of its recognition may eventually lead to organic disease.

7. General reactions may occur in spite of the absence of any local reaction at the site of injection and may occur even in patients refractory to the cutaneous (scratch and intradermal technics) and dry pollen ophthalmic tests.

8. The major cause of the increased incidence of general reactions with perennial treatment does not rest with the preparation of the pollen extract.

9. Twice as many adults and four times as many children experienced failure of relief with perennial as compared with the preseasonal method of treatment.

10. Fifty-eight per cent of the cases ending with failure of relief (counting only the last year) under preseasonal treatment were definitely relieved by perennial treatment, while 81 per cent of the failures (counting only the last year) under perennial treatment did well with the preseasonal method.

11. It appears quite evident from the data at hand that the claims advanced regarding the superiority of the perennial over preseasonal pollen therapy cannot be upheld. The most that can be said in favor of the perennial treatment in view of the results obtained and the dangers involved, is that it should be regarded merely as another form of pollen treatment to be administered cautiously by only qualified allergists on specially selected cases.

REFERENCES

1. Walker, I. C.: Oxford Medicine, New York, 1920, Oxford Press.
2. Stewart, Z. W.: Asthma and Hay Fever, J. Iowa M. Soc. **16**: 277, 1926.
3. Idem: Throughout the Year Treatment of Hay Fever, M. Women's J. **3**: 249, 1931.
4. Brown, A.: A New Plan for Applying the Specific Treatment of Pollen Hay Fever (Perennial Treatment). Preliminary Report, J. Immunol. **13**: 273, 1927.
5. Idem: The Perennial Treatment of Seasonal Hay Fever, J. ALLERGY **3**: 113, 1932.
6. Idem: The Diagnosis and Treatment of Hay Fever, M. Rec. **139**: 571, 1934.
7. Vander Veer, A., Cooke, R. A., and Spain, W. C.: Diagnosis and Treatment of Seasonal Hay Fever, Am. J. M. Sc. **174**: 101, 1927.
8. Kahn, I. S.: A Practical Method of Maintaining Induced Pollen Immunity, J. Lab. & Clin. Med. **13**: 77, 1927.
9. Piness, G.: Quoted by W. T. Vaughan.[10]
10. Vaughan, W. T.: Perennial Pollen Desensitization, J. A. M. A. **97**: 90, 1931.
11. Figley, K. D.: The Continuous Method of Hay Fever Treatment, J. ALLERGY **2**: 39, 1930.
12. Idem: Hay Fever Treatment; Continuous Method, Ohio State M. J. **29**: 360, 1933.
13. Unger, L.: Perennial vs. Preseasonal Treatment of Hay Fever, J. ALLERGY **3**: 548, 1932.

14. Colmes, A.: The Perennial Treatment of Hay Fever, J. Lab. & Clin. Med. **19**: 481, 1934.
15. Thommen, A. A.: Asthma and Hay Fever, Coca, A. F., Walzer, M., and Thommen, A. A., Springfield, 1931, Charles C. Thomas.
16. Peshkin, M. M.: Discussion of paper by L. Unger.[13]
17. Coca, A. F.: The Preparation of Fluid Extracts and Solutions for Use in the Diagnosis and Treatment of the Allergies With Notes on the Collection of Pollens, J. Immunol. **7**: 163, 1922.
18. Peshkin, M. M.: XI. A Dry Pollen Ophthalmic Test in Pollen Asthma and Hay Fever Patients Negative to Cutaneous Tests, J. ALLERGY **3**: 20, 1931.
19. Idem: Asthma in Children. I. Etiology, Am. J. Dis. Child. **31**: 763, 1926.
20. Walker, I. C.: Observations on Hay Fever, Ann. Otol. Rhin. & Laryng. **31**: 660, 1922.
21. Idem: One Hundred Cases of Apparently Cured Pollen Hay Fever, J. A. M. A. **90**: 750, 1928.
22. Rackemann, F. M.: Ultimate Prognosis in Hay Fever, Am. J. M. Sc. **177**: 333, 1929.
23. Brown, A.: The Use of Glycerolated Pollen Extracts in the Treatment of Hay Fever, J. ALLERGY **4**: 468, 1933.
24. Cooke, R. A., and Stull, A.: Preparation and Standardization of Pollen Extracts for Treatment of Hay Fever, J. ALLERGY **4**: 87, 1933; Cooke, R. A., Vander Veer, A., and Barnard, J. H.: The Treatment of Hay Fever With Standardized Pollen Extracts Based on the New Unit of Protein Nitrogen, ibid. **4**: 163, 1933.
25. Peshkin, M. M., and Fineman, A. H.: Asthma in Children. VI. A Comparative Study of the Scratch and Intradermal Methods of Skin Testing, Am. J. Dis. Child. **34**: 815, 1927.

DISCUSSION

DR. LEON UNGER.—I believe that results in our perennial method of treatment are at least as good as those with preseasonal treatment. I intend to continue the perennial treatment with as many patients as will let me do so.

Reactions in our perennial cases have been much fewer than in the preseasonal cases. We give injections once in two weeks, and the dose is a little less than the peak dose reached before the hay fever season starts. In my experience I have yet to see one of those general irritative reactions which Dr. Peshkin describes except that in a few patients a sort of an eczematous condition of the skin occurred following the injections. This condition can occur from preseasonal as well as from perennial treatment.

DR. SPIVACKE.—If Dr. Peshkin had not told us more than just this one point that the perennial method of treatment cannot be used indiscriminately, he has told us enough. After treating many hay fever patients for several years, preseasonally and also perennially, one naturally encounters many experiences. The systemic reactions that are experienced by some patients, even after they have received the perennial treatment for many years, are sometimes both startling and surprising. This method of treatment, notwithstanding the favorable reports and opinions of some authors to the contrary, is certainly not one that can be recommended to the general practitioner as a safe method for the treatment of all hay fever patients. At best only a selected group of patients can tolerate the perennial method.

Another important point is that belief in the permanency of the hay fever cure by reason of the absence of skin reactions after perennial treatment has been administered for some time, is not true in most cases. Only lately I have had one such patient who had no treatment for some time and showed no reactions whatever to skin tests. Upon the injection

of the prescribed dose, she had a very severe constitutional reaction, so that she had to be removed to the hospital where she was confined for more than two weeks.

I repeat that the perennial treatment, as has been described, is not an easy method and cannot safely be administered by the average practitioner; and second, that the absence of skin reactions following the perennial treatment is not a guide for the further treatment of such patients without encountering constitutional reactions.

DR. DUKE.—I feel sure that the dealing out of fixed methods of therapy in pollen cases by commercial houses always has been and always will be a thorn in the flesh of physicians who practice allergy and realize that patients differ in their reaction to pollen and that treatment has to be modified according to the demands of the patient and according to his reactions. It seems to me that the elaboration and perfection of the perennial method of treatment of pollen disease are destined to be the salvation of the subject. In my work it has been difficult for me to keep my patients under the preseasonal treatment for more than three seasons regardless of the result I obtain. Even though they are benefited and relieved, they frequently do not wish to continue treatment beyond a certain period of years. They do not seem to object so much to perennial treatment when they can come in at odd times and get their injections. If this treatment is given by an experienced physician who understands the patient and the therapeutic methods, I do not believe there is any danger from reaction. I do think, however, that this method demands an admixture of vasoconstrictants and should always be given distal to a tourniquet. This should make the method almost foolproof. It makes it possible for the physician to control and keep uniform the rate of absorption of pollen from the site of inoculation.

May I ask Dr. Peshkin a question? Did I understand you to say that you could dry test a person's eye and get a negative reaction and still conclude that he can react to the minute amount of pollen in the air? Also, did you say that almost all hay fever is caused by pollen? I should think the results you report would prove that there are things other than pollen that cause allergy and might affect some of the patients who give a negative eye test and yet react to something in the air.

DR. VAUGHAN.—Dr. Peshkin remarks that after the first few articles on perennial treatment there has been nothing out recently. Several persons have written on perennial treatment. There has been, so far as I know, nothing in the literature particularly criticizing it. Until we have, why keep on writing about it? So some one will have to start writing again now that Dr. Peshkin has taken exception to perennial treatment.

As to the permanency of cure, I think if he will reread those articles which have been published, he will find that there is no promise of permanent cure. There is the idea that this method gives the greatest promise of permanent cure. I am still using perennial treatment along with preseasonal and coseasonal treatment. I still get my best results from perennial treatment.

Possibly I should ask Dr. Peshkin what he means by a constitutional reaction. If he means what I think he means, I have never seen a constitutional reaction from perennial treatment. I am wondering whether his constitutional reactions occur during the season and

whether during the season he continues with the top dose. If he does, that would explain constitutional reactions. We always drop the dose with the onset of the season.

Another thing is the size of the top dose prior to the season. If one gives 4,000 pollen units, the Noon-Freeman pollen units, throughout the year, one will not get adequate relief from perennial treatment. The dose must be pushed up prior to the season to 10,000 or preferably 20,000 pollen units. I can assure you that with that method we get better results from perennial treatment than any other method of treatment, not much better but enough to make it worth discussing. As to the permanency of cure, of course we have not gone far enough. I have patients who have gone four years since discontinuing perennial treatment and who have had no more trouble. I have had others who have had trouble the next year. I have had some who have had a return of the trouble in succeeding years and with two or three injections of coseasonal treatment have been entirely relieved and have continued to be so up to the present time.

I have seen one case of the type Dr. Peshkin describes with an irritated general reaction accompanying continued treatment, a girl who with continued ragweed treatment developed an eczema which was relieved following the discontinuance of perennial treatment. She has had no hay fever since and has had no further treatment.

Dr. Aaron Brown.—After all is said and done, the perennial treatment has stood the test of time in the hands of the many men who use it. I started my first patient on perennial treatment in 1920 and discharged him in 1925, and he has been well since.

What we do in the ordinary, preseasonal treatment is to make a diagnosis, qualitatively as the causal pollen factor, quantitatively as to the degree of sensitivity, and give injections of the extracts of the indicated pollen every five to seven days, with the purpose of bringing the patient's dosage to a maximum in his class, before the onset of the season. We continue that maximum dose throughout the season, and stop all injections when the particular pollen season is over. Whatever immunity has been built up in the patient by the preseasonal treatment, is lost to an undetermined degree, making it necessary to start the patient all over again the following year, as though the case were a new one.

What do we mean by perennial treatment? Merely the continuation of treatment after the season is over, increasing the intervals between injections to ten days, two weeks, three weeks, monthly or even longer periods. The ability to give injections at long intervals is the important part of the perennial treatment. To give maximum dosage every two weeks throughout the year as Dr. Peshkin, does not answer the purpose. It is overdosing.

I have been using this treatment since 1920, and I give my patients injections of the maximum doses at monthly or even six-week or eight-week intervals, and I propose to continue that treatment, because from my experience in the large clinics in New York University, Bellevue Medical School and Bellevue Hospital, and in my practice, I have found that my patients prefer that treatment to any other kind, because the results are better.

I have had no experience with the type of case that gives a history and is not responsive to any pollen test. I would as well treat a patient

with toxin-antitoxin who gives a negative Schick reaction as treat a case with pollen which does not respond to any pollen test.

The perennial treatment has been used by many allergists, who have reported most favorably upon it. I have used this method for many years; and because it gives better results, because treatment can be started at any time of the year, because it gives us the best hopes for permanent relief, and because it has stood the test of time, I prefer to continue to use it as long as I am able to do so.

DR. PESHKIN.—Dr. Vaughan reminds me that the words "hope of permanent cure" were employed in the papers on perennial pollen treatment. Such a statement is correct, and I was careful to quote it correctly. All the authors promised "hope of a permanent cure" with perennial treatment, and the status after fourteen years is still one of hoping. It might not be amiss to expect some concrete results.

Have you ever counted the number of pollen cases on perennial treatment recorded in the literature? How many do you think there are? Excluding reduplicated cases, the total number barely reaches 500. Does this number appear large as compared with the number of pollen cases on preseasonal treatment reported in the literature in the last fourteen years? I shall leave that to your imagination.

I have been requested to define a constitutional reaction. A constitutional or general reaction occurring during the course of pollen treatment constitutes any unfavorable symptom or symptoms following an injection of pollen antigen. The symptoms may be mild or so negligible as to escape notice or they may be alarmingly severe. A general reaction may prove fatal. A general reaction may occur within a few minutes to even two days after an injection and may be manifested by only slight sneezing or transient headache or violent asthma or dermatosis. The majority of the general reactions encountered in my series of cases occurred out of the pollen season. Those that occurred in season often appeared with reduced top pollen dosage which was frequently administered at intervals of one week.

Dr. Duke's questions have been answered in my paper.

I wish to assure Dr. Brown that I am interested only in the facts of perennial pollen treatment. Dr. Brown and those who are in accord with him are privileged to adhere to their opinions on this subject. That is their inherent right.

If I have given the impression that I no longer employ the perennial treatment, that is not correct. I wish, however, to emphasize that it be discontinued in a certain group of patients for the reasons outlined in my paper. The fact should be brought home that perennial pollen treatment is not a panacea and, moreover, it has its limitations and disadvantages.

Special Report

ASTHMA OF MAXIMUM SEVERITY BUT WITH GREAT IMPROVEMENT AFTER THREE YEARS*

CASE REPORT

FRANCIS M. RACKEMANN,† M.D., AND HANS THEILER,‡ M.R.C.V.S.
BOSTON, MASS.

THIS case is reported here because it illustrates a number of points in the management of asthma.

1. The prognosis of simple bronchial asthma is never hopeless.

2. An enormous quantity of adrenalin can be taken in frequent doses over a considerable period of time without permanent damage.

3. The record of the daily number (not the quantity) of adrenalin doses is an accurate index of the progress of the asthma.

4. The clinical importance of extrinsic factors may be impossible to evaluate.

CASE REPORT

E. B. T. was a married woman, aged forty-three years. She had had hay fever from June to October each summer since the age of twenty-nine years but never asthma until the summer of 1931 (age forty-two years) when in July and in August isolated attacks lasted a few hours each. In October, 1931, trouble began in earnest after a cold. From that time on, asthma had occurred at least once and often two or three times in every night. For a time the days were clear. She had taken ephedrine daily but no adrenalin until December, 1931.

Meantime, she was conscious of sneezing when in contact with animals and more recently had been poisoned by aspirin, a dose of which had produced a typical attack of asthma. Otherwise she was well. She had never had trouble with her nose or sinuses. There was no history of headaches or of skin lesions. She did have indigestion which she thought was aggravated by certain foods, but she could not identify the foods. The bowels were regular. Her menstruation was regular and painless. She had had only one pregnancy which ended in a miscarriage at five months. There was no history of pains in joints or muscles. Her weight had been constant at 138 pounds.

She was first seen in February, 1932. She was an active, well-developed woman of forty-three years, 64 inches tall, and weighing

*From the Anaphylaxis Clinic, Massachusetts General Hospital.
†Physician, Massachusetts General Hospital; Associate in Medicine, Harvard Medical School.
‡Instructor in Comparative Pathology, Harvard School of Public Health.

138 pounds. She was apprehensive and disturbed about the future of the asthma, perhaps because she was tired from the regular recurrence of asthma every night. The skin was clean and of good color. The teeth were false except for three poor lowers. The tonsils were present but small. The pharynx was not dry, and there was no postnasal discharge. The nasal mucosa was normal in color and thickness. The chest outline was normal. The heart was normal in size and position, and the sounds were clear. There were frequent extrasystoles. The blood pressure was 130/90 mm. The lungs were clear with breath sounds of normal quality and with no râles anywhere. The abdomen and extremities were normal. The urine had a specific gravity of 1.012 and contained the slightest possible trace of albumin in a fresh specimen.

Skin tests by the scratch method showed positive reactions to cat hair and guinea pig hair, to orris powder, to ragweed in 1:100 dilution, and to maple pollen in crude dry form. Certain foods reacted a little, notably egg yolk, potato, and celery, and a retest made a month later showed the same slight reactions.

For treatment, the cat was removed, all orris powder was taken away, a strict "elimination diet" (Rowe's Diet, Nos. 1 and 2),[1] which incidentally removed eggs, potato, and celery, was instituted, and a course of treatment with cat hair extract and orris extract was started. She was encouraged to use adrenalin and was asked to keep a record of the number of individual doses taken each day. Chart 1 shows her progress graphically.

A month later she was less discouraged, but her asthma continued, requiring adrenalin in 2 to 5 doses each day. The strict diet had been discontinued after a week because it made no change. Skin tests with domestic dusts, feathers, kapok, and house dust all showed small reactions, and a rubber mattress and pillow had been provided, also without change.

In April, examination showed the lungs still free of râles in the daytime—there was no evidence of bronchial infection. The blood contained 5,000,000 red cells, 7,100 white cells, and no eosinophiles.

Dr. F. L. Weille examined her nose and throat and found a bilateral maxillary and ethmoid sinusitis. X-ray examination showed thickening of all sinus membranes. He advised, however, that operation be considered only as a last resort.

After 11 doses of cat hair extract at weekly intervals with moderate local reactions (these doses are not recorded on the chart) without noticeable improvement, the treatment was changed to timothy and red top pollen but there was no reaction to large (1:500) doses.

On April 21, 1932, she caught a cold and the adrenalin doses rose to 9 a day. Her asthma became constant, and its severity increased until her condition became alarming.

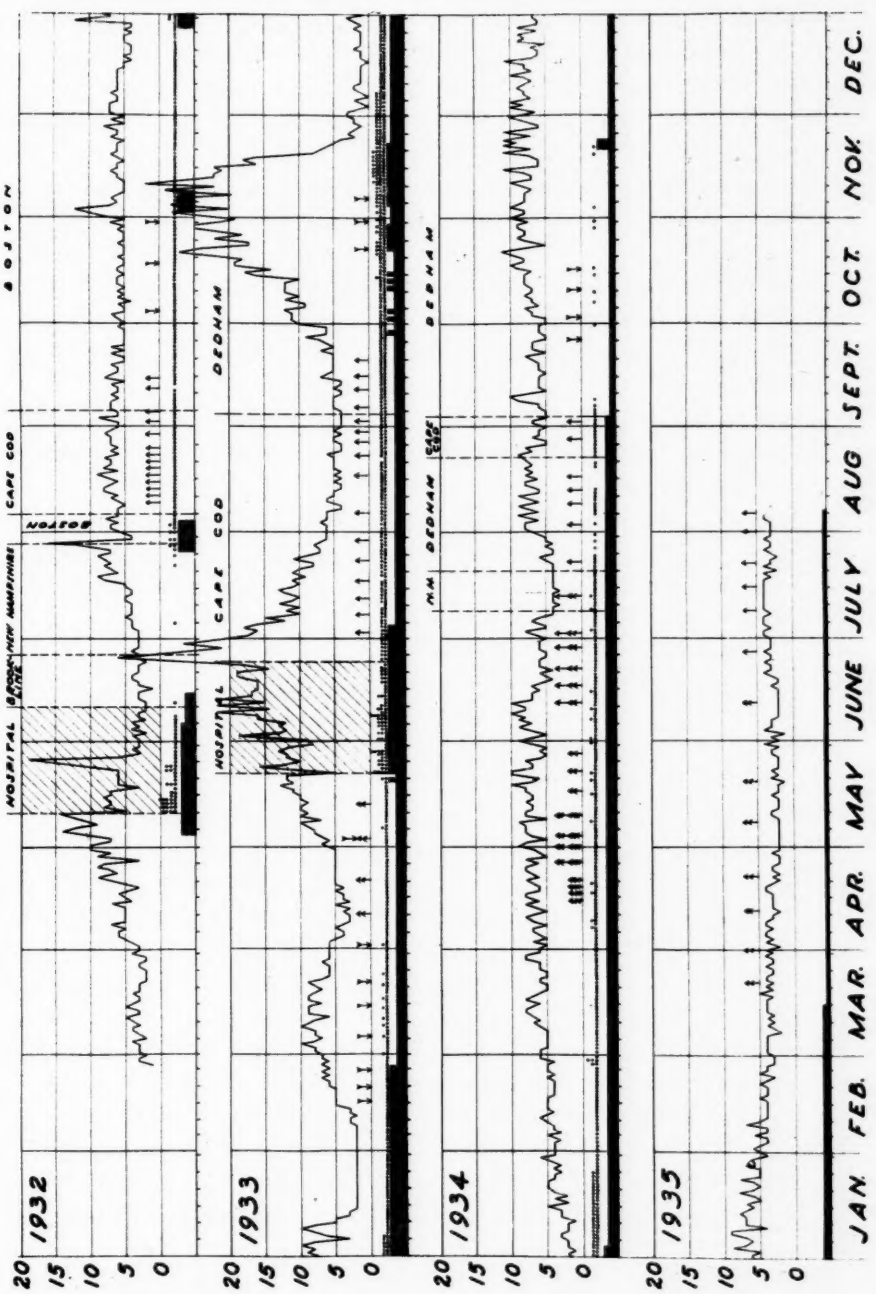

Chart 1.—The progress of Patient E. B. T. The curve shows the daily number of doses of adrenalin. The base line has dots noting five-day intervals. Changes in environment are indicated by heavy abscissae (see text). The black line below indicates activity, the heavy line meaning bed rest and the light line full activity. Dots are individual doses of pantopon each ½ grain. Inoculation treatment is shown by arrows. Upright arrows are pollen extracts; single heads for ragweed, double for grasses, and triple for trees. Arrows pointing down are vaccines. Combined treatment has a combined arrow (see text).

On May 10, she was admitted to the Baker Memorial Hospital. The white count was 21,700, but still there were no eosinophiles. For four days her food was limited to liquids without milk but then was changed to everything except eggs, wheat and milk. For two weeks the asthma continued unabated, and an oxygen tent became necessary. Pantopon was necessary from 2 to 5 doses a day. The white count was still high at 19,700. X-ray examination showed "no evidence of disease in the chest except for a slight elevation of the left diaphragm." On May 26 her temperature rose to 100.2°, and with that asthma became less. The three remaining teeth were extracted. Finally, the asthma moderated sufficiently to justify her discharge on June 10.

She moved to the suburbs (not her home) where she could sit out in the garden. Here she continued to improve although still requiring 3 to 4 doses of adrenalin in twenty-four hours. On June 25 she was taken to the mountains of New Hampshire where she learned to walk again and once covered two and a half miles. A slight sneeze was not troublesome. Soon, however, she became worse. Adrenalin doses climbed rapidly to 9 and soon to 16. Pantopon was resumed. On July 28 the situation became acute rather suddenly and she had to be brought home, arriving in a state of exhaustion after a long and hectic drive. Pulse was 120, temperature was 100°, and the lungs were full of râles. Next day, adrenalin doses dropped from 16 to 4, and for three days she could sleep and rest. Soon, however, her asthma began again.

August 5 she moved to a one-room cottage on Cape Cod. Here she improved so that she could be out every day, sitting in a rowboat or on the beach and walking short distances, but adrenalin doses ranged from 6 to 8 in twenty-four hours, and she required pantopon every day. She was eating everything, including eggs, wheat, and milk. There were no sneeze and no eye symptoms, and when late in August and in September other patients had ragweed hay fever, Mrs. T. was better rather than worse. Meantime, she had had, since August 5, 14 doses of ragweed extract reaching 0.15 c.c. of the 1:100 dilution with local reactions measuring 4 to 5 cm. in diameter. In spite of a rather large skin test, the evidence of clinical sensitiveness to ragweed was small (or was it that the desensitization treatment had been very effective?).

Back home in September and October, her asthma remained stationary with 5 to 6 doses of adrenalin and 1 dose of pantopon each day. The white count was down to 12,800, and the eosinophiles were up to 4 per cent. In November and December skin tests were made by the scratch method to a considerable variety of foods and dusts. Positive reactions were found to ragweed and cat hair. The orris was almost negative. Orange, banana, carrot, oat, and cheese gave

positive readings, and a number of other foods gave doubtful reactions. The doubtful reactions to potato, celery, and egg yolk obtained a year before were now negative. Her diet was arranged not only to eliminate all the positive and doubtful foods but to restrict her diet to those foods which gave flatly negative reactions. She remained on this limited diet for seventeen days (December 12 to 29) and did well, her adrenalin curve remaining at 4 to 5 doses in twenty-four hours.

Suddenly, on December 27, all symptoms became aggravated. She caught a cold at a party (she did *not* break her diet). For the next three weeks she was seriously ill at home, running a low grade fever up to 101°, a pulse rate between 100 and 130, and a white count around 20,000. There were râles in both bases, diffusely scattered and not localized. Sputum contained a pneumococcus Type IV. From January 12 to February 6, adrenalin was needed in only 2 doses per day. As usual, the acute infection had an excellent effect on the asthma.

In February her general condition improved but asthma increased. The adrenalin curve rose to 5 and 7 doses in twenty-four hours. A vaccine from her own pneumococcus was made, and doses were given intravenously. These materials did not help her, and on one or two occasions they produced a slight chill with fever to 102°.

In April, 1933, more skin tests to pollens showed no reaction to the common trees, very slight reactions to grasses, and the same positive one to ragweed. In spite of these negative tests, she had been so sick in 1932 that any procedure which offered hope of preventing trouble in May and June seemed justified. Treatment with timothy and red top pollen extracts was begun but without local reactions until the 1:500 dilution was reached. She did well for a time, but on May 17 she became definitely worse, and six days later she was admitted again to the Baker Memorial Hospital (about a year after the last time). Her condition was serious, if not desperate. Adrenalin no longer helped her. Three doses of pantopon at night relieved her only a little. The greatest benefit came from the slow intravenous injection of 800 c.c. of 5 per cent glucose in saline with 1 c.c. of 1:1,000 adrenalin in the mixture. At the hospital, her room was arranged with rubber mattress and pillow, and the air was filtered. The diet for the first few days consisted only of liquids without milk.

Even under these conditions intended to exclude foreign dusts and questionable foods, the asthma continued, still requiring 15 or more doses of adrenalin and 3 to 4 doses of pantopon in each twenty-four hours. The white count ranged between 10,000 and 13,000 with eosinophiles increased for the first time—5 per cent and once to 17 per cent. Study of kidney function showed a very slight trace of albumin with phthalein of 50 per cent and N.P.N. of 27 mg. per 100 c.c. She lost weight from 138 to 110 pounds.

On June 23, she went direct to Cape Cod, to the same house as in 1932. Here the asthma continued in severe form, requiring up to 20 doses of adrenalin each day. Within a few days, however, she improved rapidly and in late July was able to pick berries. Ragweed treatment begun in June was resumed. In August and September she was still doing well with no tendency to relapse in the ragweed season.

In September she was back in a small but new and modern house in the suburbs and for three weeks remained comfortable. In October, however, asthma became bad again and continued severe all the fall. In late October and November her condition was again alarming with adrenalin injected 25 and more times in twenty-four hours, and obviously without much effect. It seemed impossible to alleviate the dyspnea. We are grateful to Dr. Edward G. Thorpe for his great help during this trying period. Dr. Thorpe tried to find local signs of pneumonia but with no success. In spite of the absence of fever, we all presumed that this bad attack depended upon an infection of some kind. Soon, however, she improved, and about that time a new bed with hair mattress was obtained.

Through the winter, she did pretty well, taking adrenalin in 3 to 6 doses per day. She gained weight from 115 to 120 pounds. Was this happy period the aftermath of the infection or did it depend upon the change in bedding?

In March, 1934, skin tests made by both scratch and intradermal methods showed the usual large reaction to ragweed; the scratch test was positive to the 1:5,000 dilution. Orchard grass and red top showed a slight response to the intradermal test but not to the scratch test. Kapok reacted. Eggs, wheat, milk, oat and corn were negative. Scratch tests with pollens in dry crude form showed no reaction to any of the 18 common New England pollens except ragweed and a slight reaction to dandelion. In particular, elm, birch, oak, and sweet vernal grass were negative, but since experience had shown trouble in May of each year, she was given doses of elm and birch with sweet vernal and red top added later. Local reactions were small even to the 1:100 extracts. Perhaps, however, in spite of the negative skin tests and the lack of reaction to subcutaneous doses, this treatment helped her. The fact is that this time—in May, 1934—her asthma increased hardly at all and her general condition remained good. She did not have to be hospitalized. In spite of the need for 6 to 9 doses of adrenalin in twenty-four hours, she could do her own housework. In July she went to New Hampshire for a visit and without difficulty. In August she spent twelve days at Cape Cod and did well except for the continued use of pantopon. Meantime, treatment with ragweed pollen extract was continued into September. Asthma remained mild and did not increase during the ragweed season. In September and October pantopon was omitted on most of the days.

In October she caught a cold with purulent nasal discharge. The adrenalin curve rose from the summer level of 6 to 8 doses up to 8 to 10 doses. Stock vaccines had been given in an attempt to ward off further infections, but each dose seemed to cause an increase in asthma, so they were omitted. Her general condition was obviously better. Her weight had come up to 130 pounds. Skin tests showed the same reactions as before.

Through the winter, improvement was slow but sure. Adrenalin averaged 8 to 10 doses in twenty-four hours, but after January it dropped to 4 and 5. The last dose of pantopon was given on January 7. In March, 1935, skin tests showed ragweed much less reactive than before; the trees and grasses entirely negative. Finally, on June 3, 1935, she passed the first night in three and one-half years without a single dose of adrenalin. In the end of May, she motored to New Jersey and in June and July to Lake Champlain and passed several days with only 3 doses of adrenalin. Her weight was 135 pounds in late June and 142 pounds in August. Blood smear still showed 7 per cent of eosinophiles. Her vital capacity was only 2.2 liters. Physical examination showed no evidence of emphysema, the breath sounds being diminished but of normal quality. The heart was regular with a blood pressure of 130/80 mm. Urine was clear, specific gravity 1.006 to 1.018, without albumin or sugar. Her general appearance and more particularly her sense of confidence in the present and in the future bear at this time a striking contrast to the poor condition and the sense of depression three and a half years before. She is no longer tired and is quite able to do all her own housework and to walk out of doors. Her actions are normal. It is fair to say that the prognosis is good.

COMMENT

1. Extrinsic factors are present in every patient with asthma, but their practical clinical importance is always difficult to evaluate. Mrs. T. presented a number of positive skin reactions, but it has not been possible to demonstrate beyond doubt that any one of the corresponding foods or dusts was really concerned with the cause of her trouble.

2. New colds and respiratory infections are always important, but their precise effect depends upon the severity and perhaps upon other factors also. On several occasions an increase of asthma was attributable directly to a new head cold. On the other hand, the occurrence of a secondary infection, severe in character and accompanied by fever, has been followed promptly by a period of marked improvement. Fever is a good sign in asthma. The fact has been the basis for many special treatments including vaccines. The systemic reaction to vaccines noted on several occasions in Mrs. T.'s case is interesting.

3. Adrenalin was used in large amounts and in frequent doses administered each day for three and one-half years. An actual tabulation of the druggist bills shows that Mrs. T. used in three years 280 ounce bottles of adrenalin which has meant a total expense of $314. This item is by no means an inconsiderable one for a family of limited income. On top of it there was the cost of pantopon and other drugs amounting to $95. Whether this constant use of adrenalin over a considerable period has had any real effect on the patient is doubtful. Starr[2] has shown that in dogs large doses of adrenalin given over a long period can result in damage to the kidney expressed during life by edema with albuminuria and cylindruria. So far, Mrs. T. has shown no evidence of kidney damage, and now that the doses of adrenalin are so much reduced, there is small risk of trouble developing. Injuries to other organs besides the kidney have been considered, but so far there is no evidence of disturbed function anywhere. Except for the last residue of asthma, Mrs. T. appears well.

4. Nervous factors must always be considered. At the start of her disease, mental depression and anxiety were rather striking features. Her husband had a good position. She was eager to help him and then became totally incapacitated. She not only was unable to work but became a heavy additional burden for him to carry. The disturbance of his sleep and rest at night was an important feature. Is it surprising that she became "nervous"? Several times the ups and the downs in her asthma occurred without obvious cause. It was easy to think of the changes as nervous but difficult to prove the thought. On the other hand, the recent marked improvement in the picture is physical in part, but it is also mental or psychologic. It is good to see hope and faith take the place of fear and despair. Nervous effects would seem to be a result rather than a cause of the asthma.

5. Nose and throat lesions are always difficult to deal with. In spite of the fact that this patient had definite evidence of trouble in all her sinuses, improvement occurred without operation. The facts in this case support the thought that thickened sinus membranes are a part of the asthma and not a cause of it.

6. Finally, this case teaches us an important lesson, that regardless of its severity or duration the prognosis in asthma of the simple type (without emphysema or heart disease) is never hopeless. With constant care and supervision of details, deliverance will come. The patient should realize that the record of experiences in previous years and attacks gives the physician a great advantage in dealing with the present attack. Certain procedures have been found helpful. They can be used again. Others are harmful, even dangerous. Mrs. T. was very sensitive to aspirin and was made worse by vaccines; yet in other patients vaccines and aspirin are often helpful. To change physicians would have been to lose this great advantage. It is for-

tunate that Mrs. T. stuck. She was a good patient. Confidence and faith by both the patient and the doctor are essential to the treatment of asthma.

In August, 1935, the patient left the United States on a long voyage to South Africa. She stood the trip remarkably well, requiring 1 and 2 doses of adrenalin per day on the ship. On arrival in South Africa, she went to live in a small town which included a research laboratory, and she has been there ever since. All through our winter (the South African summer) she continued to do well, showing no increase in asthma during the warmer weather, and with no increase in the daily doses of adrenalin. She was able to do her work indoors and to take care of a small garden out of doors. Life has become satisfactory once more.

263 Beacon Street

REFERENCES

1. Rowe, Albert H.: Food Allergy, Its Manifestations, Diagnosis and Treatment, Philadelphia, 1931, Lea & Febiger.
2. Starr, Isaac, Jr.: The Production of Albuminuria by Renal Vaso-Constriction in Animals and Man, J. Exper. Med. 43: 31, 1926.

Selected Abstracts

Asthma

UNDER THE DIRECTION OF SAMUEL M. FEINBERG, M.D., CHICAGO

Observations Upon Cardiac Dyspnea. Maddox, K.: M. J. Australia **1**: 122, 1936.

The author thinks that there are two main mechanisms in cardiac asthma. At one extreme is the type with advanced failure of the left ventricle with distended and rigid lungs, where the balance is readily disturbed in the direction of an attack by relatively innocent stimuli. The latter comes from the cerebrum through the vagus or results from a small but sudden addition to the pulmonary load, for example, from slipping into the horizontal position during sleep. At the other extreme are patients with a minor grade of failure but whose irritable nervous system allows of sudden coronary spasm, together with a spontaneous extra load on the left ventricle from general vasoconstriction. The author remarks on the presence of hypertension during the attack of cardiac asthma, differing in this wise from bronchial asthma.

Broncholiths and Stone Asthma. Pendergrass, E. P., and Lorimier, A. A.: Radiology **25**: 717, 1935.

The authors discuss the formation of broncholiths and their clinical significance. They say that calcific lesions in the lungs may be explained on any of the following possibilities: (1) secondary calcification after degeneration or necrosis due to infection; (2) calcification of aspirated foreign bodies; (3) precipitation of the osseous inorganic elements, due to excessive concentration of them in the blood, and (4) metastases of bone-forming cells. The bronchial "stones" are liable to produce infection, cough, hemoptysis, and wheezing and dyspnea. The authors warn of the probability of such pathologic conditions in cases of unexplained asthma.

The Present Status of Bronchoscopy in Bronchial Asthma. Clerf, L. H.: Ann. Int. Med. **9**: 1050, 1936.

The value of bronchoscopy in asthma and related clinical conditions is emphasized. The author believes that bronchoscopy should be given a trial in the treatment of cases of bronchial asthma that do not respond to the usual methods. He obtains the best results in patients with tracheobronchitis, excessive secretions, or bronchial obstruction. Vaccines obtained from bronchoscopically removed secretions have been found of value in bacterial asthma.

A Case of Sensitivity to Chromates. Card, W. I.: Lancet **2**: 1348, 1935.

A twenty-eight-year-old woman working in a chromium-plating factory developed asthma after five months' exposure. The asthma cleared while in the hospital. The injection of 4 mg. potassium dichromate provoked an attack of asthma. Later

the same dose of potassium chromate had a similar effect. There were no positive skin reactions to the usual allergens. Upon returning to work the symptoms reappeared. Since she has obtained other employment, there have been no further attacks.

Prognosis in Bronchial Asthma. Witts, L. J.: Lancet **1**: 273, 1936.

The author considers the danger of death in the acute attack of asthma or following a paroxysm less rare than is usually described. With respect to therapeutic results he says that 20 per cent are completely relieved, about 60 per cent are more or less improved, and about 15 or 20 per cent are resistant to treatment. Favorable features in prognosis are: the ability of the patient to cooperate completely with the physician; infrequency of attacks; early age of the patient; brief duration of the disease; and a seasonal incidence and sensitization to a single allergen. Unfavorable factors are the presence of complications, such as bronchitis, sinus disease, or emphysema, and long duration of the disease. In patients under forty years with mild or occasional asthma the mortality is probably not more than 25 per cent above the standard figures. In patients over forty years with frequent and severe paroxysms the mortality is two or three times the standard value.

Dermatology

UNDER THE DIRECTION OF MARION B. SULZBERGER, M.D., NEW YORK CITY

Dermatitis From Dyed Hair, Furs and Fabrics. Ingram, John T.: Lancet **2**: 239, 1935.

The author reports that the localization of dermatitides due to dyes sometimes leads to identification of the causative agent. Skin tests always should be employed: hair and fur dyes principally para- or metaphenylendiamin and their products. Experiments convinced the author that eczemas due to these chemicals are caused by idiosyncrasies, not sensitizations. (This is questioned by the reviewer.) Material dyes most exceptionally cause dermatitides. Symptoms are edema, particularly about the eyes, and discoloration of the skin; the former usually points to hair and fur dyes, the latter to material dyes dissolved in sweat. Psychic and general disturbances may also be encountered. Five case histories serve as examples. In conclusion, the author remarks that most dyes ordinarily employed are quite harmless; that there are no more skin diseases in dyeing establishments than in other industrial plants; and that the usual skin diseases encountered in the dyeing industry are due to personal predisposition of the individual [predisposition to sensitization—M. B. S.]. The law should take cognizance of these facts.

Anti-allergic Therapy. (Antiallergische Therapie.) Urbach, Erich: Med. Klin. **1**: 440, 476, 1935.

There are five possible methods of combating allergies—prophylaxis by elimination of the allergic factor or by keeping it at a distance, deallergization, specific, metaspecific desensitization, and antipathergic therapy, which means a nonspecific lowering of allergic reactivity. The author discusses in detail the procedures belonging to each group. It is also important for the physician to treat the allergic patient psychotherapeutically. The importance of this factor must not be underestimated.

The Rôle of Alkali in the Pathogenesis of Eczema With Special Reference to Industrial Eczema. Burckhardt, W.: Arch. f. Dermat. u. Syph. **173:** 155, 1935.

The author tested the sensitivity of the skin to the caustic action of alkali by means of patch tests of graduated concentrations of pure calcium hydroxide. He found that this sensitivity varied within wide limits. Patients exposed in their occupations to the injurious effects of alkali (plasterers, galvanizers, laundresses, etc.) all exhibit a definitely lowered threshold (nonallergic sensitivity) to alkali. Besides this they usually show an eczematous sensitivity toward various other substances used in their occupation (cement, nickel, turpentine, etc.). It is probable that primary alkali injury to the skin favors sensitization to eczematogenic substances. Considering the prevalence of alkali exposure (soap!) the diminished alkali resistance of the skin must be looked upon as a possible predisposing factor in many eczematous sensitizations. By means of a functional method (alkali neutralization curves) the author demonstrates that the skin normally possesses the function of neutralizing alkali. The author's experiments have shown that in cases of alkali hypersensitivity this neutralization process is usually retarded, and that the increased sensitivity to alkali is therefore *not* of an *allergic* nature but depends on the diminished physiologic defense function of the skin to alkali. Alkali neutralization is independent of sweat secretion and is a function of the epidermal cells. The carbonic acid emitted by the skin serves as a neutralizer. The degree of alkali resistance of the skin appears to be characteristic of the individual, and a normally or regularly diminished resistance is found only at a very advanced age, according to present findings. The figures available permit of no final conclusions.

Occurrence of Agranulocytosis During Antisyphilitic Treatment. Sprafke, H.: Dermat. Ztschr. **71:** 88, 1935.

Sprafke draws the attention of dermatologists to the fact that not only salvarsan but also bismuth may prepare the way for agranulocytosis. This is not so surprising considering the chemical relationship of arsenic to bismuth. In support of the view that this property of bismuth should be kept in mind as a possible danger in attempts to obtain curative effects by storage of the drug, the author reports a case of agranulocytosis which deviated only slightly from the picture described by Schultz. Autopsy revealed an extensive necrosis of the tonsils with invasion of the pharyngeal mucous membrane. After neosalvarsan injections (3.9 neosalvarsan) and 19.0 of casbis, the patient had developed an arsenical dermatitis followed by an abscess of the thigh most probably due to infection of the lymph glands. These symptoms subsided rapidly, but thirty-three days after the last injection of bismuth she developed a typical bismuth stomatitis followed by agranulocytosis terminating fatally. In the writer's opinion this case confirms the experimental findings of Barta, Imre, and others that a preliminary toxic condition is a prerequisite for the development of agranulocytosis. Probably the bismuth stomatitis exhausted the defensive forces of the organism.

Concerning Professional Novocain Dermatoses. (Ueber die professionelle Novocaindermatose.) Kubarew, M. W.: Sovet. Dermat. **3:** 93, 1934.

Examination of 16 dentists in a dental institute showed 4 cases of novocain damage of the skin of the fingers. Two cases were mild, incipient; and 2 were severe. The latter cases are fully described. The connection with novocain was confirmed by means of patch tests; and by disappearance of the manifestations after cessation of the employment of novocain in tooth extraction work.

Studies on the Herpes Problem. Biberstein, H., and Jessner, M.: Arch. f. Dermat. u. Syph. **173**: 48, 1935.

From their experiments on guinea pigs the authors conclude that simple reddening and swelling cannot be taken as positive results of herpes simplex inoculation. Single herpes simplex inoculation seems to protect about one-half the animals from reinfection. The herpes simplex of successfully reinfected animals is slightly delayed as compared with the majority of primary inoculated animals. Reinfection within two months after the first infection is more severe than later reinfection. Herpes simplex immunity, when present, is not locally limited but a general and systemic phenomenon. Single and repeated pox inoculation does not diminish susceptibility to herpes simplex under the given experimental conditions.

As regards skin reactions, the authors found that a positive skin test could be obtained by intracutaneous injection of a killed vaccine prepared from encephalitic rabbit brain or herpes simplex infected guinea pig brain in a considerable percentage (88.8 per cent). As the susceptibility did not run a uniform course, the number of positive reactions could be increased by repetition of the experiments. Care must be exercised not to make use of a protein foreign to the experimental animal used as a vehicle for the herpes antigen. Vaccine immune animals reacted in a much smaller percentage to herpes antigen (30.8 per cent). Repetition of the experiments in vaccine immune animals did not increase the number of positive reactions but on the contrary reduced this number. Seventy-five per cent of animals surviving vaccine and herpes gave positive reactions, and in some cases a repetition of the intracutaneous injections produced focal reactions at earlier sites of injection.

In human subjects it was found that tests in patients suffering from recurrent herpes were always positive, while normal subjects and patients suffering from nonrecurrent herpes did not react. The therapeutic effects obtained consisted in focal reactions or provocation, less violent recurrences, prolongation of herpes-free intervals during, as well as after, cessation of treatment and absence of herpes over long periods of time. Owing to the nature of normal fluctuations of recurrent herpes no definite conclusions as to permanent cures could be made. In some cases there was an increase in the number of attacks after beginning of treatment (focal reaction), displacement of the site of herpes reaction or herpetoid reactions at the site of inoculation (isomorphes stimulatory effect isomorpher Reizeffekt).

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., BROOKLYN

Studies in Synergy: The Synergic Action of Staphylotoxin and Beef Lens Extract in Rabbits. Swift, H. F., and Schultz, M. P.: J. Exper. Med. **63**: 703, 1936.

The writers confirmed the findings of Burky that the antigenicity of beef lens is markedly increased in rabbits by the action of staphylotoxin. They found, moreover, that this effect was not based upon a conjugation or intimate association of the poorly antigenic lens with the strongly antigenic toxin, for the separate injection of the two substances at intervals of several hours, whether given focally or intravenously, produced the same results. Rabbits actively immune to the toxin responded to the combination of toxin and lens in the same

manner as normal rabbits responded to the lens without the toxin. The neutralization of the toxin with antitoxin in vitro before injection did not impair its synergic action on the antigenicity of the beef lens, even when injected one-half hour before the lens extract. All these findings seemed to indicate that the stimulating effect of the toxin was on the antibody producing cell rather than on the antigen.

The sensitivity of the injected animals in the above experiments was measured by precipitin, cutaneous, and ophthalmic tests.

Studies in Synergy: Synergic Stimulating Effect of Hypersensitivity to Foreign Protein and to Bacteria. Swift, H. F., and Schultz, M. P.: J. Exper. Med. **63**: 725, 1936.

Experiments were performed to study the synergic influence of hypersensitivity to indifferent streptococci and to horse serum on the antigenicity of beef lens. It was found that a combination of streptococci and beef lens, incubated together, increased the antigenic power of the lens. The same effect was obtained when the bacterial growth and lens extracts were injected separately into the animals but into the same areas. Their simultaneous injections into different foci reduced the antigenic powers of the lens extract. Focal injections of lens extract with the streptococci more strongly sensitized the rabbits than did intravenous injections of the same materials.

The synergic action of the streptococcic hyperergy did not equal that of the staphylotoxin described in the previous communication.

In animals sensitized to horse serum, the intracutaneous injection of horse serum and beef lens increased the antigenicity of the lens, regardless of whether both antigens were injected together or into different areas. The synergic action of horse serum hypersensitiveness was not so great as that exerted by streptococci.

The sensitivity induced by homologous lens injections in the rabbit was much less than that which was induced with heterologous (beef) lens.

The Agglutinogens M and N in Allergic Conditions. Harley, David: Brit. Jour. Exper. Path. **17**: 143, 1936.

The author investigated the frequency of the agglutinogens M and N in a series of 200 patients suffering with asthma and associated illnesses. Types M, N, and MN occurred in the relative frequencies of 32.0, 19.5, and 48.5, respectively. These figures disclose no deviation from normal incidences of these agglutinogens in the general population.

Further Studies on the Influences of Regional Differences in Intracutaneous Testing. Schmidt, W.: Klin. Wchnschr. **14**: 738, 1935.

In these studies intracutaneous tests were performed with 0.1 c.c. of the test solutions. Histamine was employed in a dilution of 1:1,000. The allergic reactions were read in fifteen minutes, and those with histamine in five. The results were compared on the basis of the largest diameters of the wheals.

On the arm, the tests were injected at the midpoint of the acromium-olecranon line, and also at 8 cm. above or below this point. In 13 tests with histamine, the reactions nearest the elbow were found to be the larger in almost every instance. In seven comparative tests with specific allergens, however, no such uniformity of results was obtained. In three, the upper test was the larger, in two the lower, and in two no difference could be noted.

Tests were also prepared on the back, close to and parallel with the spine. They were inserted at the level of the spine of the scapula, at 8 cm. above and at 8 and 16 cm. below this point respectively. It was found that the reaction above the scapula was almost always smaller than the rest. There was little difference between the reactions at and below the level of the scapular spine.

A Theory Concerning the Mechanism and the Significance of the Allergic Response. Vaughan, W. T.: J. Lab. & Clin. Med. **21**: 629, 1936.

The author presents a new theory of allergic response. He considers it an integrated reaction complex, which is fundamentally purposeful and protective in nature, but defective in execution, since it lacks coordination and a directing influence. "It is in essence, a manifestation of environmental maladjustment." He is of the opinion that all persons are potentially allergic, and that the response of the allergic individual differs from that of the nonallergic "in degree not in kind." Heredity and the nature of the excitant, as well as the severity of the exposure, are the outstanding factors which determine susceptibility. He cites the following as examples of the protective purposeful natures of allergic symptoms: The sneezing and the secretion of mucus in hay fever represent an attempt on the part of the organism to remove a harmful irritant; the cough, smooth muscle spasm, and increased bronchial secretion in asthma represent an attempt to remove foreign bodies from the lungs; vomiting in gastrointestinal allergy is for the purpose of expelling an offending substance; the serous exudation in contact dermatitis represents an effort to wash away an irritant, etc. When the stimulus comes from within and there is no single localized excitation, however, the response may occur in any or all of the protective tissues or fluids of the body. When certain tissues are more highly reactive than others, symptoms involving these tissues are likely to predominate.

The writer contends that the reactive bodies are the same in allergy and immunity. In the latter state, however, there is an efficient protective reaction, while in the former they behave abnormally in a disoriented, disorganized fashion.

Under the circumstances he believes more attention should be centered on the nonspecific approach to the problem of allergy in an attempt to control this "perverted disoriented reaction of protection." The field of endocrinology and that dealing with the autonomic nervous system seem to him to hold the most promise.

Otolaryngology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

Experiences With Spleen Extract in the Treatment of Allergic Diseases. Griebel, C. R.: Ztschr. f. Laryng., Rhin., Otol. (Teil 1: Folia otolaryng) **26**: 105, 1935.

Griebel reports satisfactory results in uncomplicated cases of vasomotor rhinitis by treatment with spleen extract. With the improvement of symptoms there was a disappearance of blood eosinophilia. In chronic cases of hay fever and of bronchial asthma with no eosinophilia, it was possible to produce it by means of subcutaneous injections of spleen extract although a reduction of symptoms occurred. It is believed that spleen extract exerts a regulating influence on the eosinophilo-poiesis of the bone marrow.

Effect of Hot Foot Baths on Vasomotor Rhinitis: Observations by Means of the Epinephrine Probe Test. Muck, O.: Ztschr. f. Hals-, Nasen- u. Ohrenh. 37: 357, 1935.

Muck studied the effect of hot foot baths on vasomotor rhinitis as determined by means of the epinephrine probe test. By this test he was able to differentiate two vasomotor reflex processes of the nose; the normal reaction and the so-called white streak sign. It was noted that hot foot baths produce in persons who have a normal vasomotor reaction to the epinephrine probe test a reversal of this reaction: that is, the white streak sign. In vasomotor rhinitis patients in whom the test produces a normal reaction, hot foot baths cause a preponderance of the sympathicotonus or the white streak sign. The observation was also made that hot foot baths will reduce or completely counteract attacks of vasomotor rhinitis.

Zinc Ionization in Nasal Allergy. Bernheimer, L. B.: J. A. M. A. **106**: 1980, 1936.

Bernheimer made a study of the clinical results obtained by ionization of the nasal mucosa in a group of 25 individuals with hyperesthetic rhinitis and 10 with seasonal hay fever as compared with a similar group treated by the use of escharotics. The observations extended over a period of fifteen months. It is noteworthy that two patients suffering from hyperesthetic rhinitis developed anosmia following ionization treatment which persisted for four and seven months, respectively. In another instance a neuritis of the nasal ganglion with the typical pain syndrome described by Sluder persisted for three and one-half months. No complications were noted following the use of escharotics.

From these studies it was concluded that the histologic effects of ionization do not differ from those resulting from the application of escharotics. In neither was there marked evidence of fibrosis. It was found that the clinical course of hyperesthetic rhinitis was influenced in only 5 per cent of the 25 patients who were treated with ionization. Slightly better results were obtained with escharotics. The clinical course of hay fever was not altered by the use of either method. Finally, it was stated that ionization of the nasal mucous membrane may be followed by complications which do not occur with the use of escharotics.

Rhinorrhea in Children, With Special Reference to the Posttonsillectomized Child. Persky, A. H.: Arch. Ped. **53**: 1, 1936.

Persky made an investigation of the causes of rhinorrhea in children, especially in those who had already had the tonsils and adenoids removed. Especial reference was, therefore, made to those children who gave a history of frequent colds and nasal discharge and who continued to have these symptoms after the tonsils had been removed. It was noted that certain systemic conditions may have a direct influence in these children. Reference was made to syphilis and other hereditary stigmas. In the malnutritional or marasmic group of cases, it was noted that frequent colds continued because of a lack of proper attention to this factor. Tuberculosis, diabetes, rickets, and other conditions were also considered in this group. Treatment to combat the nutritional factor was advocated. Another group of cases was considered as of the lymphatic or endocrine type, often complicated by such conditions as otitis media, asthmatic bronchitis, rheumatism, and nephritis. Finally, attention was called to the importance of proper diagnosis and treatment of the allergic type of nasal disturbances. The importance of the recognition of complicating infection

was also stressed. Various types of local treatment were also recommended. In all children with rhinorrhea, regardless of whether they fall into any of the above mentioned groups, the possibility of the nasal manifestations of allergy should always be carefully considered.

Nonspecific Therapy of Vasomotor Rhinitis. Riegele, L.: Ztschr. f. Laryng., Rhin., Otol. (Teil 1: Folia oto-laryng.) **26**: 148, 1935.

Riegele reports favorable results in the treatment of vasomotor rhinitis by the intracutaneous injection of a mixture of cresol free from protein. Wheals were induced at two-day intervals until from six to eight were made. This form of nonspecific shock therapy was effective in some instances in which other measures had failed.

Pediatrics

UNDER THE DIRECTION OF FRANCIS S. SMYTH, M.D., SAN FRANCISCO

Common Allergic Disorders in Childhood. Adams, H. B.: J. Pediat. **8**: 544, 1936.

The author presents a review of the diagnosis of allergy in childhood, discussing the importance of family history, environment, dietary factors, and specific skin tests. A very good suggestion is his classification of asthma in three types, i.e., those with inhalant or food sensitivity, those with probable infectious origin, and those with a mixed etiology. He finds mixed respiratory vaccines in properly graded doses of value in the infectious asthma though he avoids discussion as to specificity. The usual allergic skin manifestations are recognized. Much of the author's material is not new, but those unfamiliar with allergy will find it a clear, reliable guide on the subject.

The Prophylaxis of Allergic Disease. Glaser, J., and Landau, D. B.: J. Pediat. **8**: 470, 1936.

This is a rather theoretical discussion of the rôle of inheritance and the placental transmission of allergy with implications regarding prophylaxis. Some of the suggestions regarding food and environment are valuable, as are also the implications regarding future vocations of allergic children. The reviewer, however, finds sweeping applications of all the principles difficult, since some allergic manifestations (Vaughan's minor allergies) are very prevalent and often most transitory, deserving then, no great concern.

Miscellaneous

Hyperergic Phenomena and Histamine. Gotsch, K.: Ztschr. f. klin. Med. **129**: 593, 1936.

Gotsch reviewed the theory of allergy wherein the formation of histamine or a histamine-like substance is presumably responsible for symptoms. He did further experiments on 45 allergic and 82 nonallergic individuals by testing their reactions to a weak galvanic current and to histamine. He found no definite relationship between an allergic reaction and the skin reaction to electrical stimulation, for this was absent in some allergic persons and present in others of the nonallergic group. Histamine hypersensitivity likewise is apparently not an essential sign of an allergic condition. However, since histamine plays a part in the

many methods which have been recommended for nonspecific desensitization, he used it by administering the drug transcutaneously by means of a galvanic current of 8 milliamperes. The cathode was dipped in water and the anode in a histamine solution 1:20,000 and applied to the chest and forearms. The first application lasted five seconds but was gradually increased. Treatments were given daily for the first two or three weeks, and then at longer intervals. They were applied to 30 patients with bronchial asthma, 2 with migraine, 1 with hay fever and two with mucous colitis. Of the asthmatic individuals, 5 were completely relieved and 16 greatly improved. Those with migraine were entirely relieved. The author believes this method may be used not only for nonspecific treatment but as an adjuvant to desensitization.

A Case Showing an Unusual Relationship Between Asthma and Epilepsy. Costello, K., and Fox, J. T.: Lancet **1**: 660, 1936.

A child with no family history of either asthma or epilepsy began to suffer from asthma at the age of ten years; and epilepsy began at the same time. Fits occurred always at the end of an asthmatic paroxysm. As the asthmatic attacks increased, their termination was followed by major epileptiform seizures. Bronchitis was present. As the asthmatic paroxysms gradually improved, so did the epilepsy, and both disappeared at the same time.

No explanation of the phenomenon is offered other than the possibility that the cyanosis of the asthmatic attack deprives the cerebral cells of sufficient oxygen.

Allergy and Neoplasia With Special Reference to Occupational Tumor Formation. Hueper, W. C.: J. Ind. Hyg. **18**: 140, 1936.

During the course of investigation on the causative mechanism active in the production of so-called "aniline tumors" of the bladder in dye workers, evidence was obtained which seems to point to the presence of an allergic factor in the development of these neoplasms. An analysis of previous literature bearing on the subject is given in some detail.

Indications that suggest possible interrelations between allergic and neoplastic disorders include, among others, the following.

The reinoculation of homologous tumor tissue may elicit a local inflammatory reaction resembling that seen in the Arthus phenomenon.

Certain organic chemicals possess allergic and carcinogenic properties.

In the occupational field, allergic and neoplastic tissue responses may be elicited by prolonged contact with the same compounds.

In chemical allergies as well as in chemical neoplasia, epithelium and the vasculo connective tissue not infrequently form a functional unit as reacting tissue.

Other similarities of immunologic and cytologic responses in both allergy and neoplasia are stated.

Book Reviews

ALLERGY OF THE NOSE AND PARANASAL SINUSES. By FRENCH K. HANSEL, St. Louis, 1936, pp. 820, illustrated, The C. V. Mosby Co.

Although the nasal manifestations of allergy have been known to allergists for many years, curiously enough otorhinologists have but recently taken serious cognizance of them. Hence this is a new field for the nose and throat specialist, and a difficult one because the subject of allergy is inherently difficult. Constructive treatment of nasal allergy requires constitutional measures, and to administer these intelligently more than a casual conception of hypersensitiveness is required. Unfortunately, most clinicians are not well versed in immunology and pathology, so that it is difficult to secure sound understanding unless underlying principles are explained clearly and concisely.

The object of this book, as stated, is to familiarize the otolaryngologist with the clinical features of allergy as related to the field of otolaryngology, to review the various phases of the subject itself, and to point out the frequent association of allergy of the nose with allergy elsewhere. The subject matter is approached primarily by the consideration of the fundamental principles of physiology, biochemistry and bacteriology of the nasal secretions and the cellular reactions of the tissues as they relate to allergic disorders of the nose and paranasal sinuses.

It is difficult to undertake a comprehensive explanation of the subject and keep within the purpose of the book, namely to familiarize otolaryngologists with allergy as related to the field of otolaryngology. After a detailed exposition of the biologic factors, other allergic disturbances and related subjects are dwelt upon at some length. Food and gastrointestinal allergy, urticaria, erythema multiforme, angioneurotic edema, and eczema, bronchial asthma and its treatment, allergy in ophthalmology, hay fever and the chemistry of pollens all appear as chapter headings. As a consequence, the book is a comprehensive exposition of most of what is known about the subject and will serve any one who wishes to have such information available. Of particular value are the chapters on the nose and paranasal sinuses, a subject with which the author is well acquainted. It is undoubtedly the most thorough exposition in print of this phase of allergy.

This is an important contribution which allergists as well as otolaryngologists will want as a reference work.

YOUR HAY FEVER. By OREN C. DURHAM, with an introduction by Dr. Morris Fishbein and a chapter on treatment by Dr. Samuel M. Feinberg. 1936, pp. 264, illustrated. The Bobbs-Merrill Co., Indianapolis.

This book tells in narrative style the story of the development of medical and lay thought about hay fever during the past seventy-five years. The more recent knowledge concerning pollinosis, to which the author has contributed so much, notably the geographic distribution of hay fever producing plants, influence of climatic conditions, and pollen surveys, is simply and clearly stated. It is a book for the laity, and a hay fever patient would find its content of absorbing interest. The author dispels various popular fallacies and clarifies the subject. Of particular interest and value is a tabulation of ragweed pollen distribution in various cities throughout the country and the results of his recent similar studies of summer resorts. Several of these noted for their reputation as safe places for hay fever patients to sojourn evidently are more pollen laden than other less advertised localities.

Dr. Feinberg's chapter on treatment is in keeping with the simplicity of the remainder of the book. The important prophylactic and therapeutic measures are explained in understandable terms.

Allergists will welcome this book for their patients and will find much in it for their own information.